Biopolymers I

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With 131 Figures and 32 Tables

Springer-Verlag
Berlin Heidelberg NewYork
London Paris Tokyo
Hong Kong Barcelona Budapest

Polyanhydrides: Synthesis and Characterization

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The delivery of drugs from biodegradable polymeric materials for human and animal use has attracted considerable attention of investigators throughout the scientific community. Various types of polymers have been synthesized and tested for this purpose which include: poly(α-esters), poly(aliphatic esters), polyorthoesters, polyphosphazenes, poly(phosphate esters), polymers based on amino acids, natural and synthetic peptides and proteins, polysaccharides and polyanhydrides. Comprehensive reviews on various biodegradable polymers and their advantages have been published [1–5]. This chapter concentrates on the polyanhydride class of polymers.

Polyanhydrides are useful bioabsorbable materials for controlled drug delivery. They are hydrolytically unstable and hydrolyze to diacid monomers in contact with body fluids. Since their introduction to the field of controlled drug delivery, about 10 years ago, extensive research has been conducted to study their chemistry as well as their toxicity and medical applications. Several review articles have been published on polyanhydrides and the focus has been on controlled drug delivery applications [1, 2].

A major part of this chapter will review recent developments in the chemistry and properties of polyanhydrides, which includes new synthetic methods, new polymeric structures, and in depth characterization of polyanhydrides. The degradation and drug release properties and applications that were not reviewed previously are included. A review article by the same authors concentrating on polyanhydride applications and toxicity is in preparation [6].

Advances in Polymer Science, Vol. 107

Abbreviations

ACDA	acetylenedicarboxylic acid
BTC	1,3,5-benzenetricarboxylic acid
Co	drug load in gm/cc
CPH	1,6-bis(*p*-carboxyphenoxy) hexane
CPP	1,3-bis(carboxyphenoxy) propane
CPV	carboxphenoxy valerate
DMF	*N*,*N*-dimethylformamide
DSC	Differential Scanning Calorimetry
Et3N	triethylamine
FA	fumaric acid
FAD	dimer fatty acid
Gelfoam	absorbable gelatin sponge
Gliadel	Polyanhydride brain tumor implant containing BCNU
GPC	gel permeation chromatography
4HC	4-hydroperoxycyclophosphamide
IPA	isophthalic acid
Ln	average length of sequence
MIT	Massachusetts Institute of Technology
Mw	weight average molecular weight
Mn	number average molecular weight
PA	poly(adipic acid)
PAA	poly(acrylic acid)
PAZ	poly(azelaic acid)
PLA	poly(lactic acid)
PCL	poly(caprolactone)
PDP	poly(phenylenedicarboxylic acid)
PHB	poly(hydroxybutyrate)
PSA	poly(sebacic acid)
PSU	poly(suberic acid)
SA	sebacic acid
SEM	Scanning Electron Microscope
Septicin	polyanhydride antibacterial bone implant
STDA	4,4′stilbenedicarboxylic acid
Surgicel	oxidized cellulose absorbable hemostat
TA	terephthalic acid
Tg	glass transition temperature
Tm	melting point
TMA-gly	trimellitimide-glycine
ToF-SIMS	time-of-flight secondary ion mass spectroscopy
VPO	vapor pressure osmometry
Vycryl	synthetic absorbable suture
Xc	degree of crystallinity
XPS	X-ray photoelectron spectroscopy

1 Introduction

Polyanhydrides were first reported in 1909 by Butcher and Slade [7] who discovered the formation of a high melting material when isophthalic or terephthalic acid were heated in acetic anhydride. About 20 years later, Hill and Carothers [8–10] in their course of developing new useful polymeric materials for textile applications, investigated polyanhydrides of simple aliphatic dicarboxylic acids. They found that these polymers are hydrolytically unstable and degrade in room moisture. They discovered also that the polymers are thermally unstable and form cyclic dimers and polymeric rings when heated at high temperature. The research on polyanhydrides was renewed by Conix [11, 12] and Yoda [13–18] who synthesized more than a hundred new polymers based on aromatic, heterocyclic, and copolymers of aliphatic and aromatic diacid monomers that have been used in the synthesis of polyesters (Table 1). Their research was directed toward the synthesis of selected compositions designed to retain substantial hydrolytic and thermal stability and yet to have better plasticity than existing compounds as the condensation polymers like polyesters and polyamides. This goal was never reached, although there have been some progress in solving the problem. A few sporadic publications on polyanhydrides appeared during the late 1960s and 1980.

Table 1. Representative polyanhydrides synthesized during the years 1909–1980

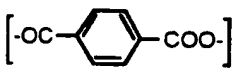
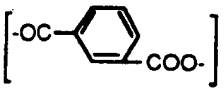
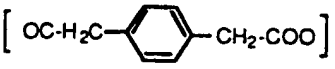
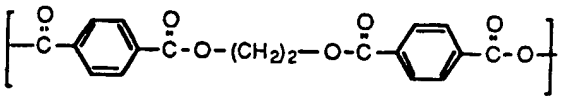
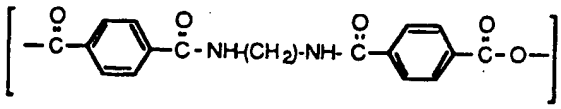
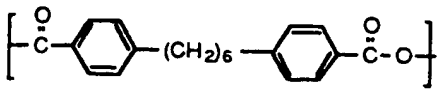
Polymer structure	Melting point (°C)	Ref.
	400	13
	256	13
	90–91	13, 16
		56
	330	13
	151	11

Table 1. (continued)

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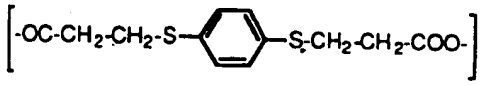
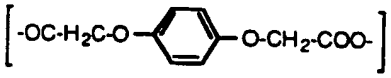
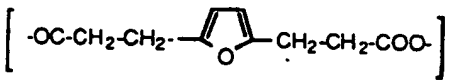
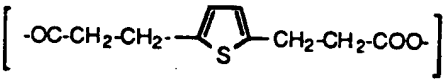
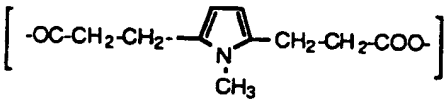
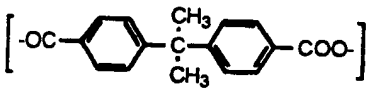
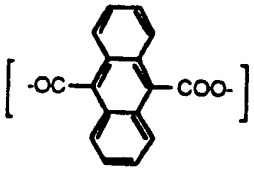
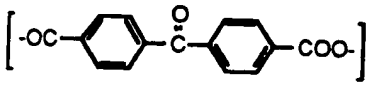
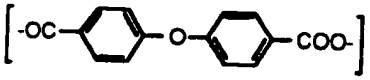
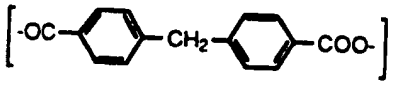
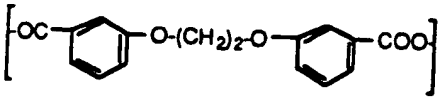
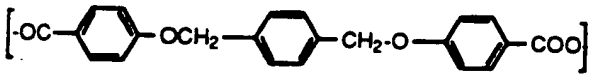
	91	13, 17
	160	70
	67	13, 14
	78	13, 14
	188	13, 14
	230	13, 14
	> 300	71
	338	72
	295	11
	332	11
	237	11
	140	73

Table 1. (continued)

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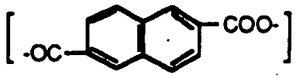
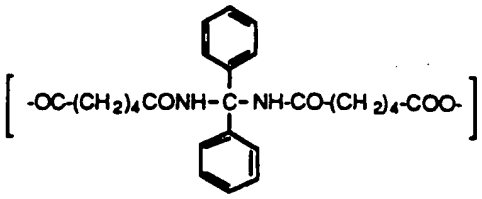
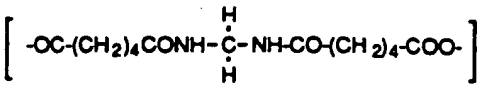
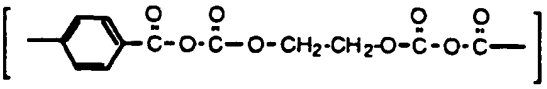
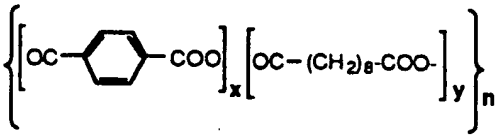
	450	72
	> 300	74
	285	74
[OC-(CH2)2-SO2-(CH2)2-SO2-(CH2)2-COO]	185	16
[OC-(CH2)2-S-(CH2)2-S-(CH2)2-COO]	81	13, 17
[OC-P-COO]		76
[OC-(CH2)x-COO] x=4-16	60–100	75
	155	37
	220	15

In the 1970s when the field of controlled drug delivery started to gain attention, the need for absorbable materials for implantable controlled drug delivery was recognized. It was only in 1980 when Langer recognized the broad potential uses of this class of polymers as biodegradable materials for drug delivery and other medical applications [19, 20]. An extensive research program on the synthesis and applications of polyanhydrides was initiated at the Massachusetts Institute of Technology (MIT) which was significantly enhanced when NOVA Pharmaceutical Corp. engaged with MIT to develop these polymers as implantable drug carriers for human use. At present, two implantable devices for human use, the Gliadel implant for the treatment of brain tumors, and the

Septicin antibacterial implant for the treatment of chronic bone infections have been developed [21–24]. The multidisciplinary concept of polymeric implants has expanded to include research on the chemistry and characterization of polymers, experimental and theoretical polymer degradation and drug release, toxicology and metabolism, and research in specific fields of applications such as cancer, proteins and hormones delivery, infectious diseases, and brain disorders. This chapter concentrates on the chemistry and characterization of polyanhydrides with a brief description on recent applications of polyanhydrides.

2 Chemistry

2.1 Synthesis

Polyanhydrides have been synthesized by the following methods: a) bulk melt condensation of activated diacids, b) ring opening polymerization, c) reaction between dibasic acid and diacid chlorides, and d) interfacial polymerization. A detailed study of these polymerization methods and various polymerization conditions for a range of diacids were previously described [25–27].

The major drawback of all previous work on polyanhydrides was their low molecular weight, which made them impractical for many applications. A systematic study to determine the factors affecting the polymer molecular weight was conducted with the purpose of synthesizing high molecular weight polymers [28]. The highest molecular weight polymers were obtained using a melt condensation process, by operating under conditions which optimized the polymerization process while at the same time minimizing the depolymerization process. Pure prepolymers were individually prepared and purified by recrystallization. The reaction conditions, reaction temperature and time, the presence of coordinative catalysts, and the vacuum applied are very important for the production of high molecular weight polymers. In addition, these polymers are chemically pure and with a determined copolymer composition similar to the entry monomer composition. This is in contrast to the polymers obtained by polymerizing unisolated mixed diacid prepolymers which are characterized as non-pure, of low molecular weight, and with unpredictable copolymer composition that can vary in the range of $\pm$ 20% from the monomer entry composition [29].

2.1.1 Melt Polycondensation

The most widely used method is the melt condensation of dicarboxylic acids treated with acetic anhydride. This method was successfully used for the syn-

thesis of aliphatic and aromatic polyanhydrides [25–28]:

$$HOOC\text{–}R\text{–}COOH + (CH_3\text{–}CO)_2O \xrightarrow{\text{reflux}} CH_3\text{–}CO\text{–}(O\text{–}CO\text{–}R\text{–}CO\text{–})_mO\text{–}CO\text{–}CH_3$$

(I)

$$(I) \xrightarrow{180\,^\circ C/0.1\ mmHg} CH_3\text{–}CO\text{–}(O\text{–}CO\text{–}R\text{–}CO\text{–})_nO\text{–}CO\text{–}CH_3$$

$$m = 1\text{–}20;\ n = 100\text{–}1000$$

The polycondensation takes place in two steps, in the first step the dicarboxylic acid monomers are reacted with excess acetic anhydride to form acetyl terminated anhydride prepolymers with a degree of polymerization (Dp) of 1 to 20, which are then polymerized at elevated temperature under vacuum to yield polymers with Dp of 100 to over 1000.

The Dp of prepolymers was affected by the nature of the monomer, the ratio between the monomer and acetic anhydride, and the reaction time. Short oligomers of 1–2 monomer units were prepared from the reaction of the diacid monomer with acetyl chloride in chlorinated hydrocarbon solution in the presence of an acid acceptor. Prepolymers were also prepared using propionic anhydride and butyric anhydride. However, these reagents boil at a higher temperature than acetic anhydride thus requiring vigorous conditions to remove the unreacted anhydride and acids by vacuum evaporation. Acetic acid mixed anhydride prepolymers were prepared also from the reaction of the diacid monomers with ketene [30].

The condensation reaction of diacetyl mixed anhydrides of aromatic or aliphatic diacids is carried out in the temperature range of 150 to 220 °C [28]. The optimum reaction temperature is 170 to 190 °C. A variety of catalysts have been used in the synthesis of a range of polyanhydrides. Some of these catalysts are listed in Table 2. Significantly higher molecular weights, in shorter reaction times, were achieved by utilizing cadmium acetate, earth metal oxides and $ZnEt_2$–H_2O (Fig. 1). Except for calcium carbonate which is a natural material, the use of other catalysts for the production of medical grade polymers is limited

Table 2. Polymerization of poly(CPP-SA) 20:80 using coordination catalysts[a]

Catalyst	Polymerization time (min)	Viscosity [n] (dL/g)	Molecular weight Mw	Mn
no catalyst	90	0.92	116800	18200
cadmium acetate	31	1.25	245000	29420
calcium oxide	20	0.88	140935	14877
barium oxide	30	0.96	185226	22500
calcium carbonate	28	0.90	141600	15500
$ZnEt_2$–H_2O (1:1)	60	1.18	199060	25312

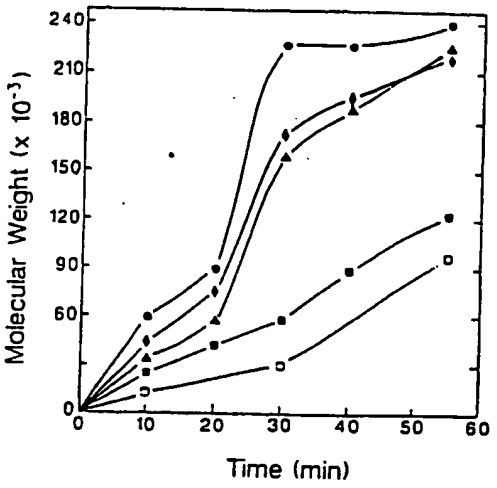


Fig. 1. Polymerization of poly(CPP-SA) 20:80 with various amounts of cadmium acetate. Polymerization at 180 °C (□) No catalyst, (■) 0.5% mole fraction, (△) 1%, (◇) 2%, (●) 3%. Molecular weight refers to weight average (from Reference [28])

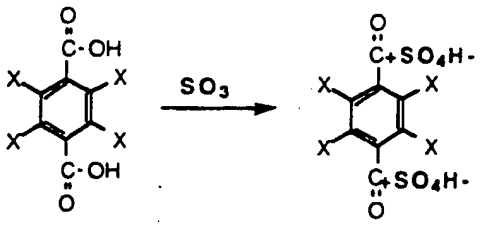
because of their potential toxicity. Prior to the use of these catalysts in biopolymers, it would be necessary to ensure the removal of the catalyst.

Polyanhydrides can be synthesized by melt condensation of trimethylsilyl dicarboxylates and diacid chlorides to yield polymers with intrinsic viscosities up to 0.43 dl/g [31, 32] :

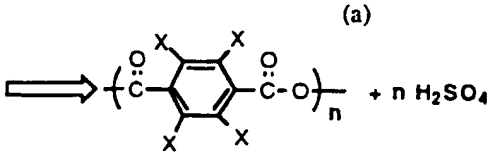
$$n\,Me_3Si{-}O{-}CO{-}R{-}CO{-}O{-}SiMe_3 + n\,Cl{-}CO{-}R'{-}CO{-}Cl$$
$$\rightarrow 2n\,Me_3SiCl + Me_3Si{-}(O{-}CO{-}R{-}CO{-}O{-}CO{-}R'{-}CO)_n{-}OSiMe_3$$

The polymerization is carried out at 100 °C under vacuum in the presence of benzyltriethylammonium chloride. This method possess several disadvantages over the acetic anhydride melt condensation method: it requires the pure chloride and the trimethylsilyl derivatives of the dicarboxylic acid monomers, and an equimolar ratio of monomers is required to affect the polymerization which makes it difficult to prepare copolymers of various ratios of comonomers. Also, the polymers obtained are of a lower molecular weight and contain trimethylsilyl or acid chloride as terminal groups.

Melt condensation of diacylium cations of tetrahaloterephthalic acids produced polymers with number average molecular weight of 10400 in high yields [9]. Solid tetrabromoterephthalic diacilium bis-bisulfate salt (a), prepared from the reaction of tetrahaloterephthalic acid and a mixture of H_2SO_4 and SO_3 in a mass fraction of 85:15, was polymerized in SO_2 at 120 °C. The polymer can be synthesized directly from the reaction of a 1:1 molar ratio of tetrahaloterphthalic acid and SO_3. Copolymers of tetrachloro and tetrabromoterephthalic acid were prepared from the reaction of the bromodisulfate and the chloro acid derivatives to yield polymers of 5000 molecular weight in 50% yield.



(a)



Direct polycondensation of sebacic acid and adipic acid at a high temperature under vacuum resulted in low molecular weight oligomers. These oligomers were used as hardeners for epoxy resins [34] :

$$n\,HOOC\text{–}(CH_2)_8\text{–}COOH \rightarrow (OOC\text{–}(CH_2)_8\text{–}CO)_n + n\,H_2O$$

$$n = 5 \text{ to } 10$$

2.1.2 Ring Opening Polymerization

In several studies on the behavior of aliphatic diacids of the structure:

$HOOC\text{–}(CH_2)_n\text{–}COOH$ where n is 4, 5, 6, 7, 8, 9, 10, 11, and 12

toward anhydride formation, Hill and Carothers reported [8–10] the formation of low molecular weight linear polymers which undergo transformations as follows:

$HOOC\text{–}(CH_2)_8\text{–}COOH \rightarrow$ α–anhydride(MW, 5000) $\rightarrow$

β–anhydride(cyclic dimers) + ω–anhydride (residue, MW, 20 000)

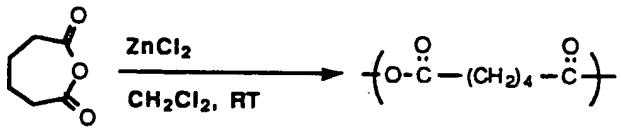
↓ standing

δ–anhydride (cyclic MW 5000)

When these polymers were subjected to molecular distillation, cyclic monomers and dimers were distilled off and a high molecular weight polymer remained behind. The cyclic molecules were transformed to a polymer on standing, this polymer is thought to contain very large ring structures. In order to distinguish the cyclic monomer from the polymer and cyclic dimer, Hill and Carothers used the reaction with aniline. Monomeric anhydride can react with aniline to give only one product, the acid monoanilide, whereas the dimer or polymer may lead to three products, the dibasic acid, the acid monoanilide and

the dianilide. The dimers are crystalline solids which polymerize instantly when heated above their melting point or upon standing. The monomers of 8, 10, and 12 atoms are very unstable and polymerize even below room temperature. The 7 atoms monomer of adipic acid is more stable but polymerizes upon heating at 100 °C for a few hours [9]. Polymerization of adipic acid diacetate prepolymers at 180 °C under vacuum yielded a polymer with a molecular weight of 14 000 that contains significant amounts of the cyclic adipic anhydride [28].

The preparation of adipic acid polyanhydride from cyclic adipic anhydride (oxepane- 2,7-dione) was investigated by Albertsson and Lundmark [35]. The monomer was prepared by the reaction of adipic acid and acetic anhydride followed by catalytic depolymerization under vacuum. The ring opening polymerization was affected by temperature, reaction time and concentration of catalyst (stannous 2-ethylhexanoate). H-NMR and IR studies indicated a non-ionic insertion polymerization mechanism at the beginning of the reaction, but after 2 hours at 80 °C, anhydride interchange appeared to be the dominating reaction which resulted in a low molecular weight polymer. The polymerization was carried out also in dichloromethane at room temperature in the presence of 1% $ZnCl_2$ and resulted in a polymer with Mn = 1700 in 75% yield [35]:



2.1.3 Solution Polymerization

A variety of solution polymerizations at ambient temperature have been reported (Scheme 1) [15, 25, 36]. Partial hydrolysis of terephthalic acid chloride in the presence of pyridine as an acid acceptor yielded a polymer of MW = 2100:

A. x HOOC–R–COOH + y Cl–CO–R′–CO–Cl

$$\xrightarrow{Et_3N/0\,^\circ C} [(OC\text{–}R\text{–}COO)_x(OC\text{–}R\text{–}COO)_y]n$$

B. n Cl–CO–R′–CO–Cl + n/2 H_2O → [CO–R′–COO]n + n HCl

C. HOOC–R–COOH $\xrightarrow{\text{dehydrat. agent}}$ $[CO\text{–}R'\text{–}COO]_n$

D. HOOC–R–COOH + Cl–CO–Cl + Et_3N

$$\xrightarrow{0\,^\circ C} [CO\text{–}R'\text{–}COO]_n + Et_3N \cdot HCl + CO_2$$

R = aliphatic, aromatic, and a heterocyclic organic residue

The use of dehydrating agents effected polyanhydride formation [25]. The use of *N,N*-bis(2-oxo-3-oxazolidinyl)phospharamido chloride, dicyclohexylcarbodiimide, and chlorosulfonyl isocyanate as coupling agents produced impure and low molecular weight polymers. The isolation and purification of the polymer from the amine acid acceptor and the dehydrative agent by-products required extraction with water which evoked hydrolytic decomposition. The reaction between diacid chloride and dibasic acid or the dimethylester derivative in pyridine-toluene or ether in the presence of $ZnCl_2$ yielded white polymers [15, 38].

Two approaches for one step solution polymerization of polyanhydrides at ambient temperature were reported [39]. In the first approach, pure polymers ($> 99.7\%$) were obtained by the use of sebacoyl chloride, phosgene, and diphosgene as coupling agents and poly(4-vinylpyridine) or K_2CO_3 as insoluble acid acceptors. The polymer is exclusively soluble in the reaction solution and the only by-product formed is the insoluble acid acceptor-hydrochloric acid salt. Polymerization of sebacic acid with phosgene either as a gas or in toluene solution, or diphosgene as a coupling agent with triethylamine or insoluble poly(4-vinylpyridine) as an acid acceptor yielded polymers with MW = 16 000. The polymer was contaminated with a large amount of triethylamine-HCl, whereas the polymer prepared with poly(4-vinylpyridine) was pure. The triethylamine-HCl by-product can be removed by extraction with water which may hydrolize the polyanhydride. The second approach was the use of an appropriate solvent where the polymer is exclusively soluble but the corresponding by-product is insoluble or vice versa. Under this condition polymerization of sebacic acid gave the best results in *N,N*-dimethylformamide and in toluene.

2.1.4 Interfacial Polymerization

Homo and copolyanhydrides were synthesized in an aqueous and nonaqueous interfacial reaction. Various aromatic polymers were prepared from the reaction of equimolar amounts of the acid dissolved in aqueous base and the corresponding diacid chloride dissolved in an organic solvent [25, 38]. Because the reaction is between a dibasic acid in one phase and an acid chloride in the other phase, the copolymers may present a regularly alternating structure. In the reaction between sebacoyl chloride in chloroform and isophthalic acid sodium salt in water a copolymer that contain mostly sebacic acid units was obtained. These results can be explained by partial hydration of two acid chloride end groups to form an anhydride bond.

2.2 Polyanhydride Structures

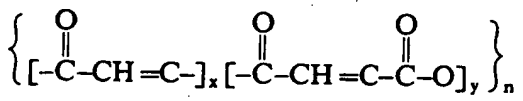
Since the discovery of polyanhydrides in 1909, hundreds of polymers have been reported [26, 27]. A representative list of polymers developed up till the end of

the 1970s is shown in Table 1. Polyanhydrides intended for use in medicine that have been developed since 1980 are discussed below.

2.2.1 Unsaturated Polymers

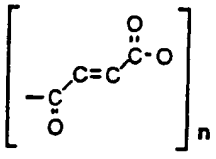
A series of unsaturated polyanhydrides were prepared either by melt or solution polymerization of fumaric acid (FA), acetylenedicarboxylic acid (ACDA), and 4,4'-stilbenedicarboxylic acid (STDA) [39, 40]. The properties of several of these polymers are listed in Table 3.

Weight average molecular weights of up to 30000 were obtained in 30 minute of polymerization, longer polymerization time resulted in an insoluble material [40]. The double bonds remained intact throughout the polymerization process and were available for a secondary reaction to form a crosslinked matrix. The unsaturated homopolymers were crystalline and insoluble in common organic solvents. Copolymers of fumaric acid and acetylenedicarboxylic acid with aliphatic diacids were less crystalline and were soluble in chlorinated hydrocarbons. The ^{1}H NMR and IR data on these polymers and the isolation of the intact unsaturated monomers after polymer hydrolysis indicated that the monomers were not altered during the polymerization process. This is in contrast to early reports by Michael and Bucher [41] and Shopov [42] which indicated a change in the monomer structure of unsaturated diacids during polymerization reaction. Michael and Bucher [21] reacted acetylenedicarboxylic acid with acetic anhydride at reflux to yield acetoxymaleic anhydride. Shopov reported the formation of polyethynyleneketoanhydride of the formula:

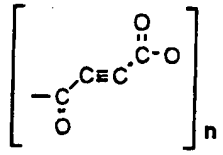


from the reaction of acetylenedicarboxylic acid with phosgene and triehtylamine

Table 3. Unsaturated Polyanhydrides



P(FA)



P(ACDA)

Polymer	Tm [°C]	Mw	Mn
P(FA)	248–250		
P(FA-SA) 1:1	99–101	20900	9100
P(FA-SA) 1:4	70–72	29350	13250
P(ACDA-SA) 1:1	77–78	11000	5700
P(STDA-SA) 1:4	102–104	36300	16200

Data taken from Ref. [40].

in chloroform at room temperature. Both investigators studied the homopolymers which are insoluble and melt at high temperatures which made it difficult to analyze them properly.

The SA-FA copolymers displayed nearly constant degradation rates and drug release rates under physiological conditions. The time for complete degradation of poly(fumaric acid) and poly(sebacic acid) occured in 2 and 15 days, respectively, while their copolymers degraded within this range. Radical copolymerization of styrene and methylmethacrylate with the polyanhydrides resulted in crosslinked insoluble polymers [40].

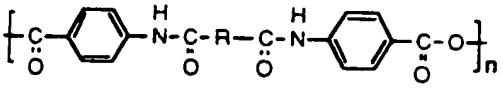
Copolymers of fumaric acid or maleic anhydride and isophthalic acid were prepared by melt condensation at 250–300 °C for 8 hours using acetic anhydride or polyphosphoric acid as dehydrative agents [43].

2.2.2 Amino Acid Based Polymers

General methods for the synthesis of poly(amide-anhydrides) and poly(amide-esters) based on naturally occurring amino acids have been described [44]. The polymers were synthesized from dicarboxylic acids prepared by amidation of the amino group of an amino acid with a cyclic anhydride, or by the amide coupling of two amino acids with a diacid chloride. This approach was demonstrated by the synthesis of polymers based on alanine and proline. The polymers were of low molecular weight as a result of azlactone formation which terminates the polymerization [44]. Low molecular weight polymers from methylenebis(*p*-carboxybenzamide) were synthesized by melt condensation [45]. A series of amido containing polyanhydrides based on *p*-aminobenzoic acid were synthesized by melt condensation. The polymers melted at 58 to 177 °C and had a molecular weight of 2500 to 12400 [46]. The properties of several of these polymers are listed in Table 4.

Eight imide-diacids synthesized from trimellitic anhydride, pyromellitic anhydride and aminoacids of the formula $HOOC-(CH_2)_n-NH_2$, with n = 1, 2, 3,

Table 4. Poly [methylenebis(*p*-carboxybenzamide)]



-R-	Tg	Tm	Mn
$(CH_2)_3$	38	58	2300
$(CH_2)_2-CH(C_4H_9)-$	150		12400
$(CH_2)_8$	102		11600
$(CH_2)_2-O-(CH_2)_8-O-(CH_2)_2$	35	88	3800
$(CH_2)_2-O-(CH_2)_6-O-(CH_2)_2$	39	114	7100
$(CH_2)_2-O-(CH_2-CH_2-O)_2-(CH_2)_2$	28	50	4800
$(CH_2)_2-O-CH(CH_3)-CH_2-O-(CH_2)_2$	37	106	6900

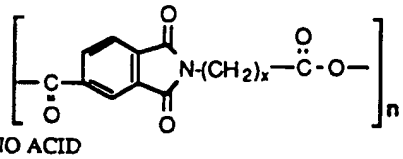
Data taken from Ref. [46].

5 were polymerized by melt polycondensation [47, 48]. These co-polyimides have an aliphatic-aromatic structure and the relation between the general properties and the amount of the aliphatic part in the repeat unit was studied. These polymers were stable at temperatures above 300 °C and were soluble in *N,N*-dimethylformamide (DMF) and dioxan. The structure of these polymers and their properties are shown in Table 5.

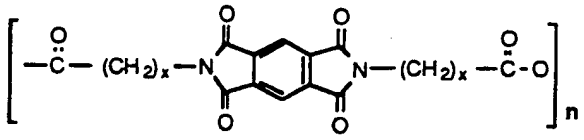
The trimellitic-amino acid polymers and its copolymers were extensively studied for use as an erodible carrier for drugs [49–51]. The following amino acids were incorporated in a cyclic imide structure to form a diacid monomer: glycine, β-alanine, γ-aminobutyric acid, L-leucine, L-tyrosine, 11-aminoundecanoic acid and 12-aminododecanoic acid. These diacids were then converted into their corresponding polyanhydrides by melt condensation. The homopolymers of all *N*-trimellitylimido acids containing amino acids were rigid and brittle with MW below 10 000 [49]. Higher molecular weight polymers were obtained by incorporation of flexible segments, i.e. copolymers with aliphatic diacids, in the polymer backbone (Tables 6, 7). Maximal molecular weight was generally obtained at 180 °C after 1 to 2 hours. Addition of earth metal oxides and metal salts, known catalysts for anhydride synthesis [28], resulted in higher molecular weight polymers in shorter reaction times.

Table 5. Poly(imide-anhydrides)

TRIMELLITIC-AMINO ACID



PYROMELLITIC-AMINO ACID



Polymer (x=)	Degradation[a] temp. (°C)	$[\eta]$[b] (dl/g)	Solubility DMF	$CHCl_3$	Dioxan
Trimellitic					
1	330	0.16	+ +	−	±
2	320	0.16	+ +	±	±
3	360	0.19	+	±	±
5	330	0.23	+ +	±	+ +
Pyromellitic					
1	365	−	±	−	±
2	312	−	±	−	±
3	347	0.17	+	−	±
5	377	0.19	+ +	±	+ +

Data taken from Refs. [47, 48] + soluble; + + very soluble; ± slightly soluble; − insoluble.
[a] 10% weight loss in a thermogravimetric test.
[b] determined in DMF at 25 °C in an Ubbelohde viscometer.

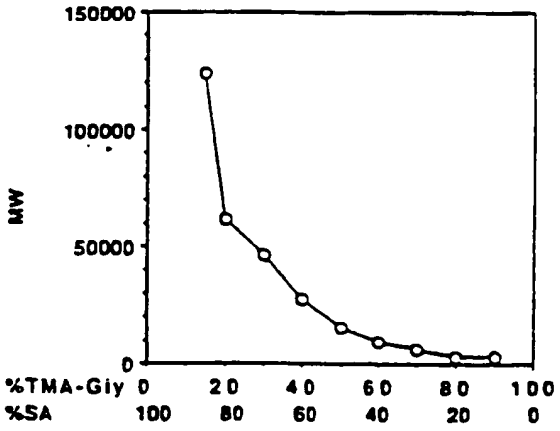
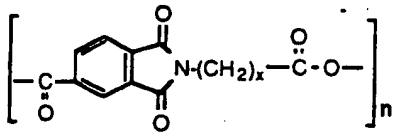


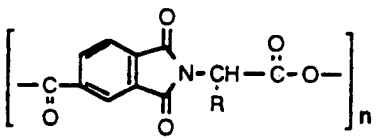
Fig. 2. Poly(TMA-gly:SA) of various ratios, melt polymerized for 2 h at 180°C (from Ref. [49])

Copolymers of *N*-trimellitylimido-glycine or aminodecanoic acid with either sebacic acid (SA) or 1,6-bis(*p*-carboxyphenoxy)hexane (CPH) were prepared in defined ratios. High molecular weight copolymers (> 100 000) were generally obtained with an increasing content of the SA or CPH comonomer (Fig. 2). Similar phenomena were found for copolymers of aromatic and unsaturated diacids with sebacic acid. Increasing content of SA or CPH also resulted in low melting polymers.

Table 6. Poly(imide-anhydride) based on trimellitic-imide diacids

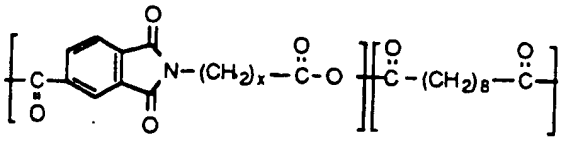


X	Tg	Mn	crystallinity (%)
1	98	< 5000	66.0
2	102.7	< 5000	
3	98.8	6500	
4	81.5	6700	
5	63.2	14800	
10	21.4	11450	66.0
11	25.9	19250	



R = -CH_2-CH-$(CH_3)_2$
R = -CH_2-C_6H_5-OH
R = -CH_2-S-CH_2-C_6H_5

Table 7. Poly(imide-anhydride) copolymers with sebacic acid



Polymer (X=)	%SA	Mw	Tg [°C]	Elongation at break [%]	Tensile strength [kg/cm²]
1	50	< 5000	29.3	44	205
2	50	21390	26	298	1872
3	50	18060	29.9	339	3531
4	0	14600	81	54	1202
5	0	12350	63	21	1890
10	47	17760	9.3	37	1069

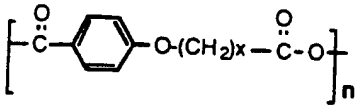
Data taken from Refs. [48–51].

2.2.3 Aliphatic-Aromatic Homopolymers

Polyanhydrides of diacid monomers containing aliphatic and aromatic moieties, poly[*p*-carboxyphenoxyalkanoic anhydride], were synthesized by either melt or solution polymerization with molecular weights of up to 44600 (Table 8) [52].

The aliphatic-aromatic diacid monomers were prepared from the reaction of bromoalkanoic acid methyl ester and p-hydroxy benzoic acid methyl ester. The polymers of carboxyphenoxy alkanoic acid of n = 3, 5, and 7 methylenes were soluble in chlorinated hydrocarbons and melted at temperatures below 100 °C. Copolymers of these monomers melted at lower temperatures than the respective homopolymers. These polymers displayed zero-order hydrolytic degradation profile ranging from 2 to 10 weeks. Increasing the length of the alkanoic chain, decreased the degradation rate of the polymer (Fig. 3).

Table 8. Aliphatic-aromatic homopolyanhydrides



X	Tm	Mw	Mn	[n]
1	204–5			
5	50–1	44600	18950	0.58
7	53–4	33300	15300	0.46
1 + 5	62–5	21800	10100	0.32
1 + 7	37–40	13630	5640	0.30

Data taken from Ref. [52].

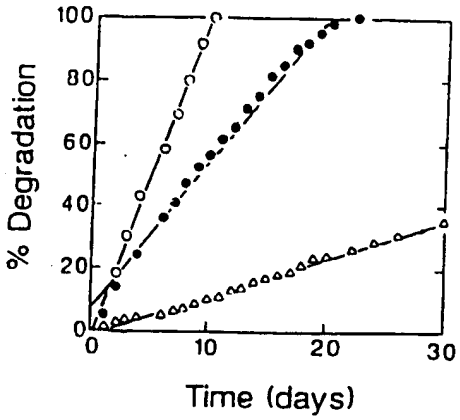


Fig. 3. Degradation of poly(ω-(p-carboxyphenoxy)alkanoic anhydrides). (o) poly(CPA), (●) poly(CPV); (△) poly(CPO) (from Ref [52])

2.2.4 *Soluble Aromatic Polymers*

Aromatic homopolyanhydrides are insoluble in common organic solvents and melt at high temperatures (Table 1). These properties limit the use of purely aromatic polyanhydrides, since they can not be fabricated into films or microspheres using solvent or melt techniques. Synthesis of soluble and low melting copolymers of common aromatic diacids have been recently reported [53, 54].

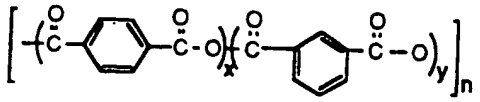
Copolymers of isophthalic acid (IPA), terephthalic acid (TA), 1,3- bis(carboxyphenoxy)-propane (CPP), or hexane (CPH), and fumaric acid (FA) were synthesized. Copolymers containing a mass fraction of 20% of a second aromatic monomer became soluble and melted at temperatures below 120 °C. The polymers had a molecular weight of 35 000. The copolymer properties were dependent on the nature and ratio of the comonomers in the polymer as seen in Table 9. Polymers of isophthalic acid containing a mole fraction of 10 to 90% fumaric acid or a mole fraction of 10 to 60% CPP were soluble, non-crystalline, and melted below 120 °C. The copolymers of terephthalic acid (TA), however, were soluble only between the mole fraction range of 15 to 40% TA content as shown in Table 10.

Table 9. Soluble and low melting aromatic copolymer compositions[a]

Copolymer of:	Compositions, % monomer	Copolymer of:	Compositions, % monomer
TA-CPP	20–30 TA	TA-SA	0–30 TA
TA-FA	10–35 TA	CPP-SA	0–65 CPP
TA-IPA	10–40 TA	IPA-SA	0–70 IPA
CPP-IPA	10–60 CPP	FA-SA	0–70 FA
CPP-FA	15–50 CPP		
IPA-FA	10–90 IPA		

[a] Polymers in this range have a solubility of > 1% in dichloromethane and melting points below 150 °C. TA- terephthalic acid; IPA- isophthalic acid; CPP- bis(p-carboxyphenoxy propane); FA- fumaric acid; SA- sebacic acid. The estimated range is in mole fractions with an error of ± 5%.

Table 10. Copolyanhydrides of terephthalic acid and isophthalic acid

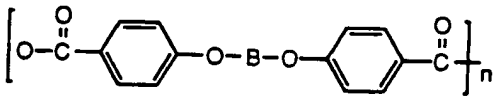


TA IPA

polymer of:	Melt. point (°C)	Crystallinity (%)	Solubility (% w/v)
TA	400	60	< 0.1
IPA	256	61	< 0.1
TA-IPA 1:4	110	< 5	20
TA-IPA 3:7	120	< 5	15
TA-IPA 1:1	230	> 30	< 1

Data taken from Ref. [53].

In a recent US patent, Ziegast described a series of polyanhydrides (of the formula shown below) which are useful for controlled drug delivery of drugs [55]. These polymers have a similar structure to the polymers synthesized by Conix (Table 1) [11, 12], but with different chain structures between the two aromatic rings. The polymers were soluble in chlorinated hydrocarbons with a Tg ranging from 6 to about 90 °C. The in vitro degradation in phosphate buffer of these polymers is about 100 days with a lag time of up to 30 days for some polymers [55]. If these homopolymers are implanted in animals, they will produce large diacid monomers which have to be eliminated from the body.



B = $-(CH_2-CH_2-O)_x$ x = 3,4; $-CH_2-CH(O-C(=O)-(CH_2)_y-CH_3)-CH_2-$ y = 1,2,8

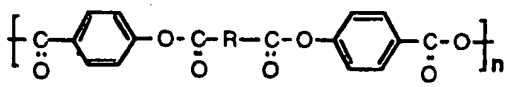
2.2.5 *Poly(ester-anhydrides)*

4,4′-Alkaline- and oxaalkanedioxydibenzoic acids were used for the synthesis of polyanhydrides [56]. The polymers melted at a temperature range of 98 to 176 °C and had a molecular weight of up to 12900 as listed in Table 11.

2.2.6 *Fatty Acid Based Polyanhydrides*

Polyanhydrides were synthesized from dimer and trimer of unsaturated fatty acids. The dimers of oleic acid and erucic acid, prepared by radical coupling via

Table 11. Ester containing polyanhydrides



-R-	Tg	Tm	Mn
$(CH_2)_2$	45	176	8720
$(CH_2)_4$	33	159	6080
$(CH_2)_8$	33	135	12900
$(CH_2)_2$–O–$(CH_2)_6$–O–$(CH_2)_2$		125	8900
$(CH_2)_2$–O–$(CH_2)_2$–O–$(CH_2)_2$		105	9300
$(CH_2)_2$–O–$(CH_2$–CH_2–$O)_2$–$(CH_2)_2$	50	110	5900
$(CH_2)_2$–O–CH_2–$CH(C_2H_5)$–O–$(CH_2)_2$		98	8550

Data taken from Ref. [56].

the double bond, are liquid oils containing two carboxylic acids available for anhydride polymerization. Table 12 summarizes the molecular weights and melting points of these polymers [57]. The homopolymers are viscous liquids, copolymerization with increasing amounts of sebacic acid forms solid polymers with increasing melting points as a function of SA content. The polymers are soluble in chlorinated hydrocarbons, tetrahydrofuran, 2-butanone, and acetone. The degradation and drug release from these polymers is discussed in Sect. 5

The properties of a polyanhydride were modified by the incorporation of long chain fatty acids, such as stearic acid, in the polymer composition which alters its hydrophobicity and decreases its degradation rate [58]. Since natural fatty acids are monofuctional they would act as polymerization chain terminators and control the molecular weight. A detailed analysis of the polymerization reaction show that up to about 10% mole fraction content of stearic acid, the final product is essentially a stearic acid terminated polymer. Whereas, at

Table 12. Typical molecular weights and melting points of Poly(FAD-SA)[a]

Polymer	Peak MP	Mw	Mn	[η]
P(FAD)	liquid	34400	8600	0.25
P(FAD-SA) 80:20	30	24400	9100	0.26
P(FAD-SA) 60:40	49	36500	14000	0.32
P(FAD-SA) 50:50	68	280000	28500	0.96
P(FAD-SA) 40:60	72	88000	20800	0.67
P(FAD-SA) 30:70	74	103700	22600	0.77
P(FAD-SA) 20:80	76	113000	20900	0.74
P(FAD-SA) 10:90	78	120400	22600	0.84
P(SA)	82	130500	23300	0.88

[a] molecular weight was determined by GPC, the melting point was determined by DSC.

higher amounts of acetyl stearate in the reaction mixture resulted in the formation of increasing amounts of stearic anhydride by-product with minimal effect on the polymer molecular weight which remained less than 5000. The rate of drug release from these polymers decreased as the stearic acid content of the polymer was increased. Mixtures of polyanhydrides with triglycerides and fatty acids or alcohols did not form uniform blends.

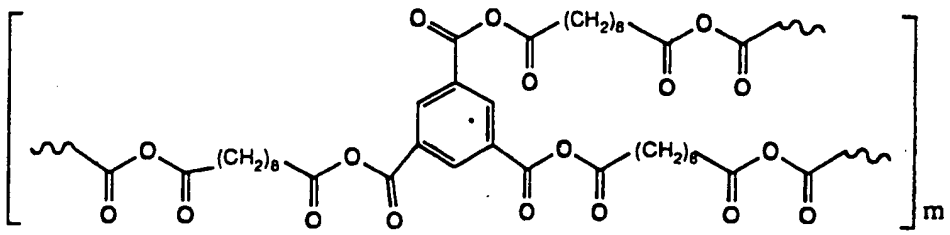
2.2.7 Modified Polyanhydrides

The physical and mechanical properties of polyanhydrides can be altered by modification of the polymer structure with a minor change in the polymer composition. Several such modifications include the formation of polymer blends, branched and crosslinked polymers, partial hydrogenation and reaction with epoxides.

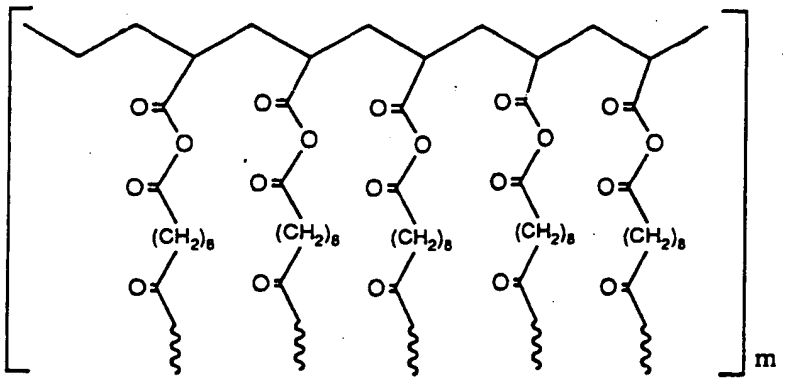
Biodegradable polymer blends of polyanhydrides and polyesters have been used as drug carriers [59]. Poly(lactic acid) (PLA), poly(hydroxybutyrate) (PHB), and poly(caprolactone) (PCL), of 2000 and 50000 molecular weights were mixed with poly(sebacic anhydride) (PSA), and the properties of these mixtures were studied. Mixtures of PHB and low molecular weight PLA or PCL formed uniform blends with various amounts of PSA. These blends possess different physical and mechanical properties compared to the parent polymers. The release rate of drugs from these polymeric blends increases with the increase in the content of the rapidly degrading component, PSA.

Branched and crosslinked polyanhydrides were synthesized by reacting the prepolymers of diacid monomers with tri- or polycarboxylic acid branching monomers [60]. Sebacic acid was polymerized with 1,3,5 benzenetricarboxylic acid (BTC) and poly(acrylic acid) (PAA) to yield random and graft-type branched polyanhydrides (Fig. 4). The polymerization was followed until the gel point, and the resulting polymers were evaluated for their physico-chemical properties and degradation behaviour. The molecular weights of the branched polymers were significantly higher (mol. wt. 250000) than the molecular weight of the respective linear polymer (mol. wt. 80000) (Fig. 5). In the case of poly(acrylic acid) branched polymers, the molecular weight increased linearly with increasing concentration of poly(acrylic acid). The specific viscosities of the branched polymers were lower than linear polyanhydrides with similar molecular weights. Except for the difference in molecular weights, there were no noticeable changes in the physico-chemical or thermal properties of the branched polymers and the linear polymer [60]. Release of morphine was much higher from the poly(acrylic acid) branched polymers compared to the 1,3,5 benzenetricarboxylic acid branched polymers and increased with increasing concentrations of the branching agent (Fig. 6).

Polyanhydrides can be transformed into poly(anhydride-esters) without degradation of the polymer. The reaction between propylene oxide and a polyanhydride yielded a poly(anhydride-ester) [43]. The reaction was carried out at



Poly(sebacic anhydride) branched with 1,3,5 benzenetricarboxylic acid



Poly(sebacic anhydride) branched with poly(acrylic acid)

* m is the number of branching molecules
~~ is a polymeric chain

Fig. 4. Structures of branched polymers (from Ref [60])

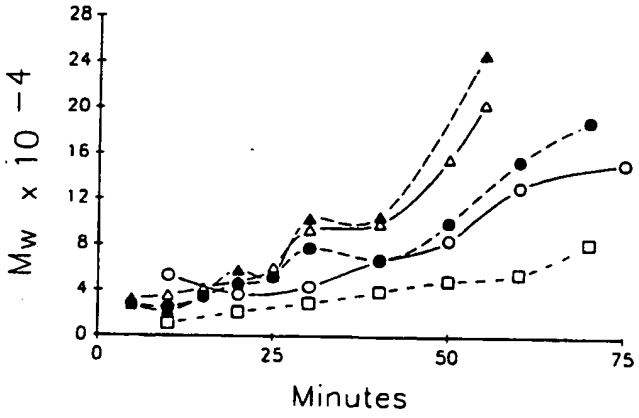


Fig. 5. Molecular weight of branched polyanhydrides; effect of the concentration of poly(acrylic acid) (PAA) branching agent on gel time, and molecular weight. (□) 0%; (○) 0.5% (●) 1.0%; (△) 1.5%; (▲) 2.0%. (from Ref [60])

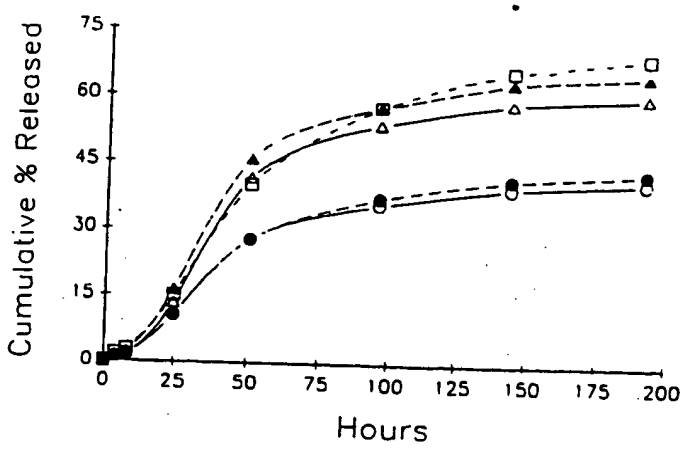
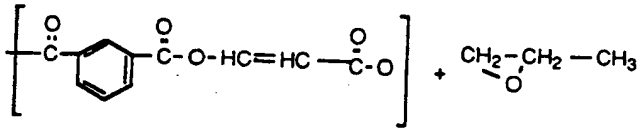
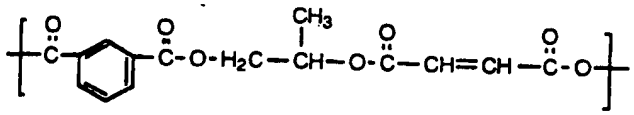


Fig. 6. Release of morphine from randomly branched polyanhydrides; effect of the concentration of the branching agent, benzenetricarboxylic acid (BTC) on the cumulative release of morphine. (□) 0%; (○) 0.5%; (●) 1.0%; (△) 1.5%; and (▲) 2.0% (from Ref [60])

60 °C/69 kPa in an autoclave with propylene oxide and triethylamine/propylene glycol as catalyst as follows:





The polymer of molecular weight range from 1500 to 3000 was polymerized with styrene via the double bonds to form a crosslinked composite.

3.1 Characterization

In the past decade, extensive research has been carried out on the characterization of polyanhydrides. This section will describe the methods used for the characterization of polyanhydrides and data obtained about their chemical composition and structure, crystallinity and thermal properties, mechanical properties, and thermodynamic and hydrolytic stability.

3.1.1 Composition by ^1H NMR

The composition of polyanhydrides has an important role in enabling different erosion rates of these polymers. The composition and structure of polyanhydrides has been determined by NMR, Raman, and IR spectra analysis [61–64], and by masspecrometry, SIMS, and XPS [65, 66].

The polymer composition and the sequence of the comonomers can be determined by ^{1}H NMR as demonstrated in the analysis of the aromatic-aliphatic homopolymers [52]. The aliphatic-aromatic diacids can be connected in a polymer in three ways, aliphatic moiety to aliphatic moiety, aliphatic to aromatic, and aromatic to aromatic moieties. The ^{1}H NMR spectra of the carboxyphenoxy valerate (CPV) diacetate prepolymer and polymer are shown in Fig. 7. The methylenic protons of the aliphatic residue conjugated to the anhydride bond in the polymer appeared as two triplets (e) at 2.54 ppm and 2.72 ppm chemical shifts. The aromatic protons *ortho* to the anhydride bond appeared in two chemical shifts (a), a doublet at 7.90 ppm and at 8.10 ppm. The peaks at 2.72 and 8.10 were not observed in the spectrum of the prepolymer (Fig. 7). These peaks were explained by a chemical shift effect across the anhydride bond, affecting the absorbancies of the α-protons to the anhydride bond. These peaks were attributed to the three types of anhydrides present in the polymer: the 2.54 ppm signal corresponds to the aliphatic-aliphatic anhydride bond, 2.72 ppm to aliphatic-aromatic, and 8.10 ppm to aromatic-aromatic anhydride bonds. Examination of the integration of these peaks revealed a ratio of 1:2:1, aliphatic-aliphatic, aliphatic-aromatic, and aromatic-aromatic moieties. This ratio implies an equal statistical distribution of alternating aromatic-aromatic and aliphatic-aliphatic units throughout the polymer backbone [52].

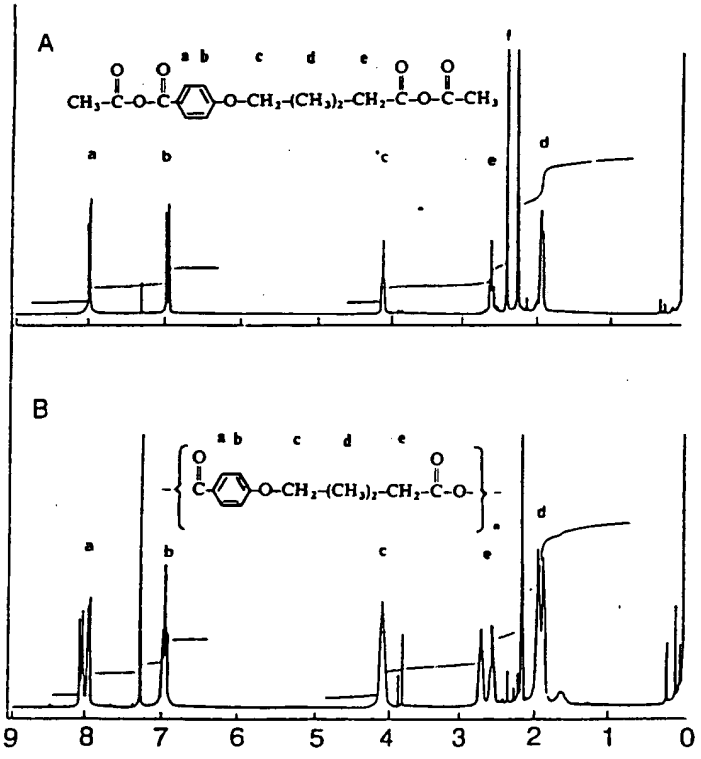


Fig. 7. H NMR spectra (in ppm) of (A) CPV prepolymer, (B) poly(CPV) (from Ref [52])

A detailed study on the use of NMR to identify statistical segments in a polyanhydride chain was reported by Ron et al. [61]. The following copolymer characteristics were studied: 1. the degree of randomness that suggests whether the polyanhydride is either a copolymer or a mixture of homopolymers, 2. average length of sequence (Ln), and 3. frequency of occurrence of specific comonomer sequences. Copolymers of carboxyphenoxy propane (CPP) and sebacic acid (SA) were used as model polymers (Fig. 8). As observed in the aliphatic-aromatic polymers described above, the protons close to the electronegative groups, as the aromatic comonomers, experience a lower density of shielding electrons and absorb at lower frequency. On the other hand, the protons next to aliphatic comonomers, absorb at higher frequency. Accordingly, the CPP-CPP and CPP-SA diads were represented by peaks at 8.1 and 8.0 respectively, and the triplets at 2.6 and 2.4 represent the SA-CPP and SA-SA diads, respectively. By integration of the ^{1}H NMR spectra of poly(CPP-SA) of various compositions the degree of randomness, average block length, and the probability of finding the diad SA-SA or SA-CPP were calculated as shown in Table 13 and Fig. 9.

Similar data analysis was applied also to copolymers of sebacic acid with fumaric acid [40], CPH [61], and trimellitimide derivatives [51]. Based on the ^{1}H NMR analysis, a FA-FA or SA-SA dimer alternating structure (-SA-SA-FA-FA-SA-SA-FA-FA) was suggested for P(FA-SA) 1:1. In the case of copolymers of the asymmetric trimellitimide comonomer (represented by the letters B1 or B2) with the symmetric comonomers sebacic acid or CPH (represented by the letter A), 6 diad sequences were expected to be present in the polymer backbone (A-A, A-B1, A-B2, B1-B1, B1-B2, B2-B2) and they were identified by ^{1}H NMR spectroscopy. Due to partially overlapping peaks in some of the copolymers, some assumptions were made. A typical data from this analysis is shown in Table 14.

3.1.2 Molecular Weight

The molecular weight of polyanhydrides was determined by viscosity measurements and gel permeation chromatography (GPC) [61]. Attempts to determine the molecular weight using vapor preasure osmometry (VPO) were not successful as discussed below. The weight average molecular weight (Mw) of polyanhydrides range from 5000 to 300 000 with a polidispersity of 2 to 15 which increases with the increase in Mw molecular weight. The intrinsic viscosity [η] increases with the increase in Mw.

The Mark-Houwink relationship for poly(CPP-SA) was calculated from the viscosity data and the Mw values, as determined by universal calibration of the GPC data using polystyrene standards:

$$[\eta]^{23\,^\circ C}_{CHCl_3} = 3.88 \times 10^{-7} Mw^{0.658}$$

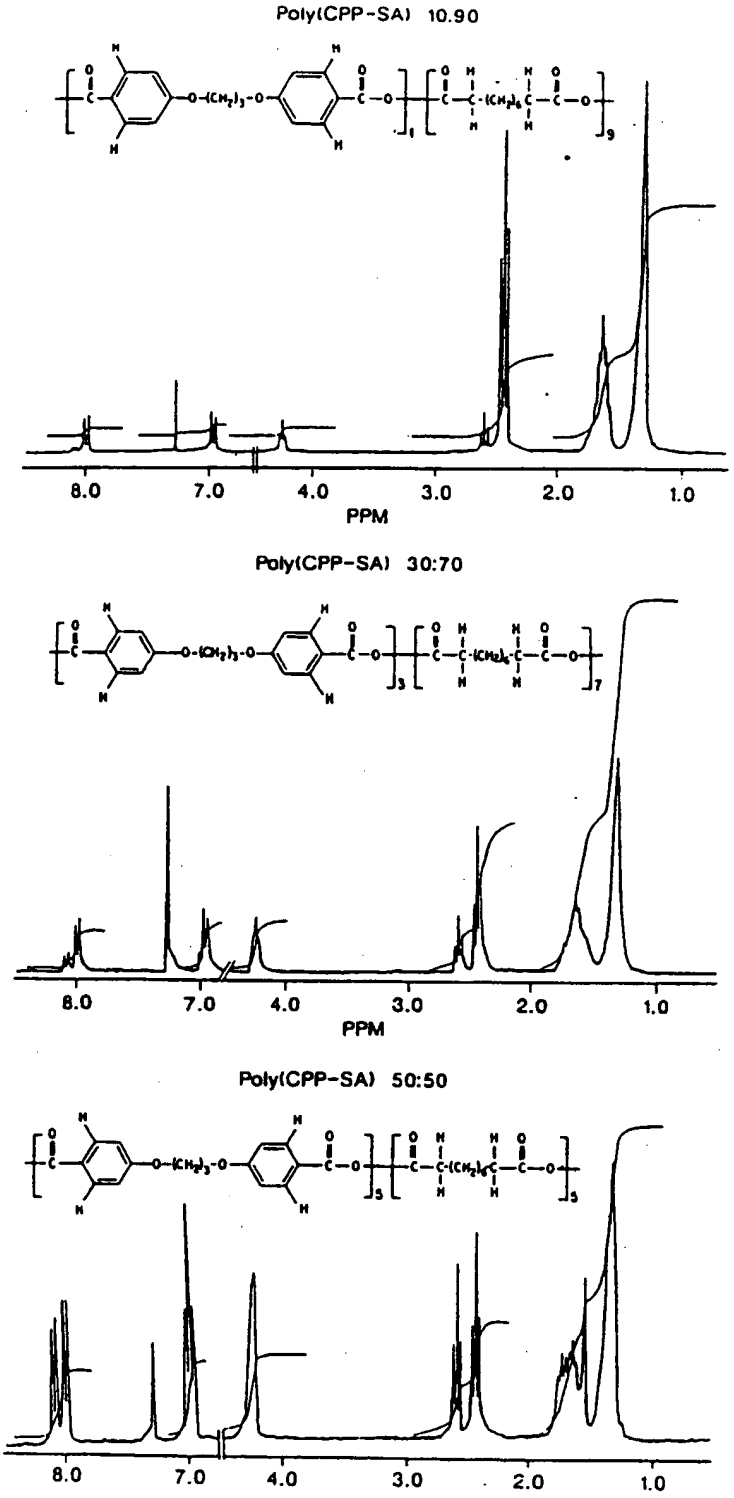


Fig. 8. H NMR spectra (in ppm) of CPP-SA copolymers (from Ref [61])

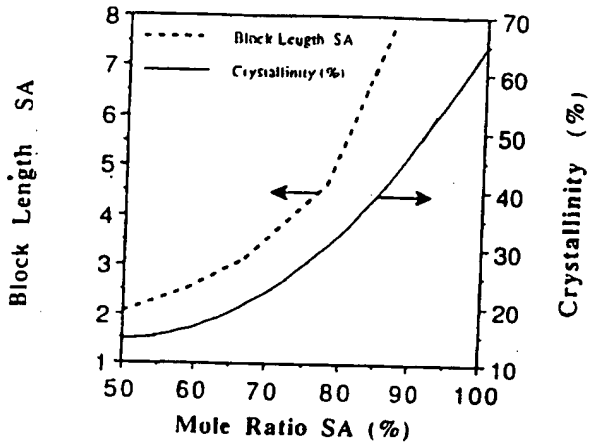


Fig. 9. Crystallinity, the average block length of SA vs mole fraction of SA for poly(CPP-SA). (from Ref [61])

Table 13. Comonomer sequence distribution of the poly(CPP-SA) series

mole ratio of SA-CPP in the polymer, p(SA)	probability of finding the diad SA-SA, p(SA-SA)	probability of finding the diad SA-CPP, p(SA-CPP)	average block length L(SA)	degree of randomness
0.96	0.86	0.14	12.3	0.3
0.87	0.76	0.22	7.8	0.4
0.82	0.67	0.30	5.5	0.6
0.63	0.45	0.36	3.5	0.7
0.59	0.36	0.47	2.5	0.9
0.49	0.24	0.49	2.0	1.0

Data taken from Ref. [61].

Table 14. Observed diad probabilities in copoly(trimellitimide-glycine: sebacic acid) (TMA-gly:SA) of various ratios

%TMA-gly	%SA	PSA-SA	PSA-B1	PSA-B2
0.00	1.00	1.00	0.00	0.00
0.11	0.89	0.906	0.051	0.043
0.30	0.70	0.800	0.100	0.100
0.47	0.53	0.579	0.211	0.211
0.60	0.40	0.115	0.471	0.414

Data taken from Ref. [51].

The universal calibration concept for GPC was confirmed for poly(CPP-SA). The acetic acid end group determination for molecular weight estimation was not used because the polymer may contain cyclic macromolecules with no acetate end groups [28].

Attempts to determine the Mn using VPO resulted in a decrease in the polymer molecular weight during measurements. At a given concentration and

temperature, the polymer sample being measured is expected to reach equilibrium in approximately 1–3 minutes. An increase in the VPO readings, as exhibited by the aliphatic polyanhydrides, indicated a decrease in molecular weight during measurements as revealed by GPC analysis of samples taken during VPO determination.

3.1.3 Crystallinity

Since crystallinity is an important factor in controlling polymer erosion, analysis of the effect of polymer composition on crystallinity was studied [61, 62]. Polymers based on sebacic acid (SA), (*p*-carboxyphenoxy)propane (CPP), (*p*-carboxyphenoxy)hexane (CPH), and fumaric acid (FA) were investigated. The crystallinity was determined by: 1. X-ray diffraction, 2. a combination of X-ray and DSC, and 3. data generated from ^{1}H NMR spectroscopy and Flory's equilibrium theory. Homopolyanhydrides of aromatic and aliphatic diacids were crystalline (> 50% crystallinity). Copolymers possess high degree of crystallinity at high mole ratios of either aliphatic or aromatic diacids. A typical X-ray powder diffraction of CPP-SA copolymer series is shown in Fig. 10. The heat of fusion and crystallinity of poly(CPP-SA) is shown in Table 15. The glass transition, Tg, the melting point, Tm, and the heat of fusion were determined by DSC. The crystallinity, Xc, was calculated from the DSC and X-ray powder diffraction. Heat of fusion values for the polymers demonstrated a sharp decrease as CPP is added to SA or viceversa. The trend of decreasing crystallinity, as one monomer is added, appeared using the X-ray or DSC methods. The decrease in crystallinity is a direct result of the random presence of other units in the polymer chain. A detailed analysis of the copolymers of sebacic acid with the aromatic and unsaturated monomers, CPP, CPH, FA, and trimellitic-amino acid derivative was reported [51]. Copolymers with high ratios of SA and CPP, TMA-gly, or CPH were crystalline while copolymers of equal ratios of SA and CPP or CPH were amorphous. The poly(FA-SA) series displayed high crystallinity regardless of comonomer ratio.

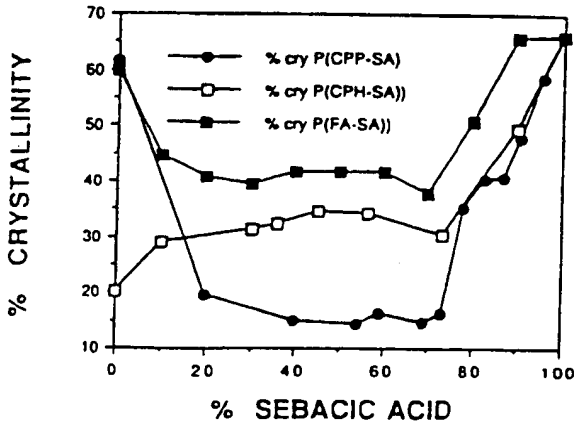


Fig. 10. Percent crystallinity of P(CPP-SA), P(CPH-SA), and P(FA-SA) polymers. (from Ref [61])

Table 15. Heat of fusion and crystallinity of poly(CPP-SA)

Polymer	Tm °C	Tg °C	Heat of fusion cal/g	Crystallinity Xc %	Wc %
Poly(SA), 100%	86.0	60.1	36.6		66.0
poly(CPP-SA) 4:96	76.0	41.7	24.9	46.5	58.7
poly(CPP-SA) 9:91	78.0		25.7	48.5	58.7
poly(CPP-SA) 13:87	75.0	47.0	20.7	39.5	40.5
poly(CPP-SA) 17:83	72.0	47.0	19.3	37.0	40.2
poly(CPP-SA) 22:78	66.0	47.0	15.3	30.0	35.0
poly(CPP-SA) 27:73	66.0	44.0	10.2	20.0	16.2
poly(CPP-SA) 31:69	66.0	40.0	5.1	10.6	14.5
poly(CPP-SA) 41:59	178.0	4.2	2.0	4.0	16.2
poly(CPP-SA) 46:54	185.0	1.8	3.1	6.1	14.2
poly(CPP-SA) 60:40	200.0	0.2	6.0	13.9	15.0
poly(CPP-SA) 80:20	205.0	15.0	8.2	17.6	19.5
poly(CPP), 100%	240.0	96.0	26.5		61.4

Data taken from Ref. [61]. Tm, Tg and heat of fusion were determined by DSC. The crystallinity was determined from the X-ray diffraction and the heat of fusion.

3.1.4 Infra Red and Raman Analysis

Anhydrides present characteristic peaks in the IR and Raman spectra. In general, aliphatic polymers absorb at 1740 and 1810 cm^{-1} and aromatic polymers at 1720 and 1780 cm^{-1}. A typical IR spectra of aliphatic and aromatic polymers that contain aliphatic and aromatic anhydride bonds may present 3 distinct peaks, where the aromatic peak is shown at 1780 cm^{-1} and the aliphatic peaks at 1720–1740 cm^{-1} in general overlap. The presence of carboxylic acid groups in the polymer can be determined from the presence of a peak at 1700 cm^{-1}. The degradation of polyanhydrides can be followed by IR from the ratio between the anhydride peak at 1810 and 1700 cm^{-1}. The significance of this analysis is that it measures the hydrolysis of the anhydride bonds and not the dissolution of the degradation products which is dependent on the solubility of the degradation products.

The Raman spectra for a variety of polyanhydrides was studied by Davies et al. [63, 64]. The Raman spectra of polyanhydrides were similar to the IR spectra for the same compounds. Polyanhydrides show two distinctive carbonyl Raman bands corresponding to the symmetric and asymmetric vibrations of the carbonyl groups, the separation of the pair being generally 50–70 cm^{-1}.

Fourier-Transform Raman Spectroscopy (FTR) was used to characterize a homologous series of aliphatic poly(anhydrides), poly(carboxyphenoxy)alkanes, and copolymers of carboxyphenoxy propane (CPP) and sebacic acid. All anhydrides show two diagnostic carbonyl bands, the aliphatic polymers has the carbonyl pairing at 1803/1739 cm^{-1}, and the aromatic polymers have the band pair at 1764 and 1712 cm^{-1}. All the homo- and copolymers showed methylene bands due to deformation, stretching, rocking and twisting; the spectra for the

aromatic poly(anhydrides) such as P(CPP) also showed diagnostic benzene para-substitution bands. It was possible to differentiate between aromatic and aliphatic anhydrides bonding and in conjunction with other diagnostic bands to monitor the change in individual monomer composition within a copolymer mixture.

Fourier transform Raman (FTR) was used to study the hydrolytic degradation of polyanhydrides [63]. PSA rods exposed to water for 15 days were analyzed daily by FTR (Fig. 11). The carbonyl anhydride band pair (1803/1739 cm^{-1}) diminished in intensity from day zero to 15, with the emergence of the complimentary acid carbonyl band (1640 cm^{-1}) which increased in intensity over the same period. Similarly, the increase in the intensity of the C–C deformation at 907 cm^{-1} with hydrolysis reflects the increased freedom of the methylene chain in the low molecular weight oligomers.

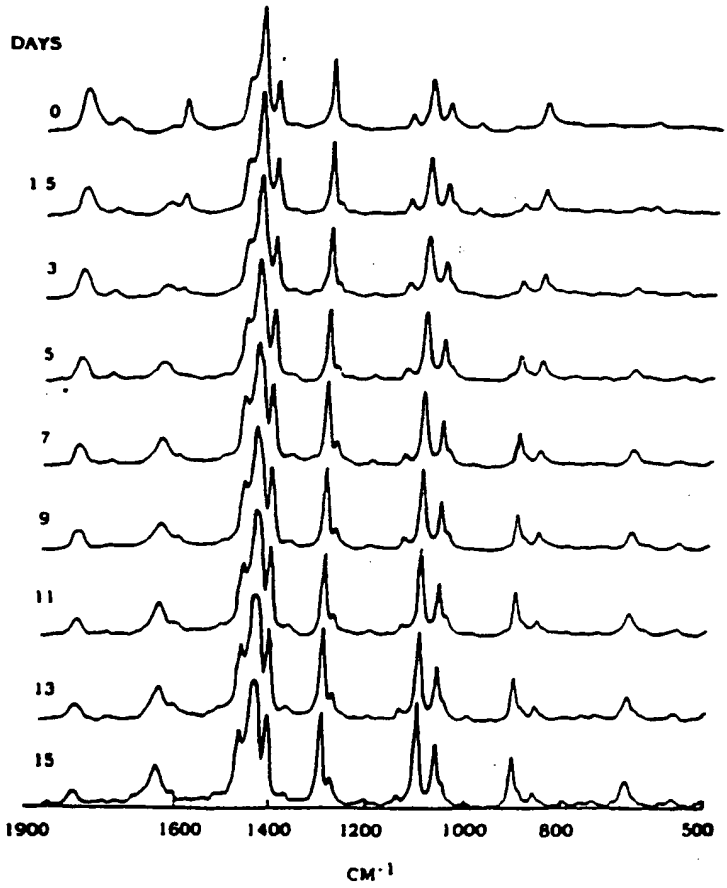


Fig. 11. Raman spectra of PSA at various time intervals during a degradation study. Note change in peak sizes at (in cm^{-1}) 1803/1739 (anhydride); 1640 (acid); 907 (monomer); 850 (polymer) (from Ref [63])

3.1.5 Surface and Bulk Analysis

The morphology of polyanhydride was studied by Scanning Electron Microscope (SEM) to elucidate the mechanism of polymer degradation and drug release from polyanhydrides [67]. Microspheres prepared by three different

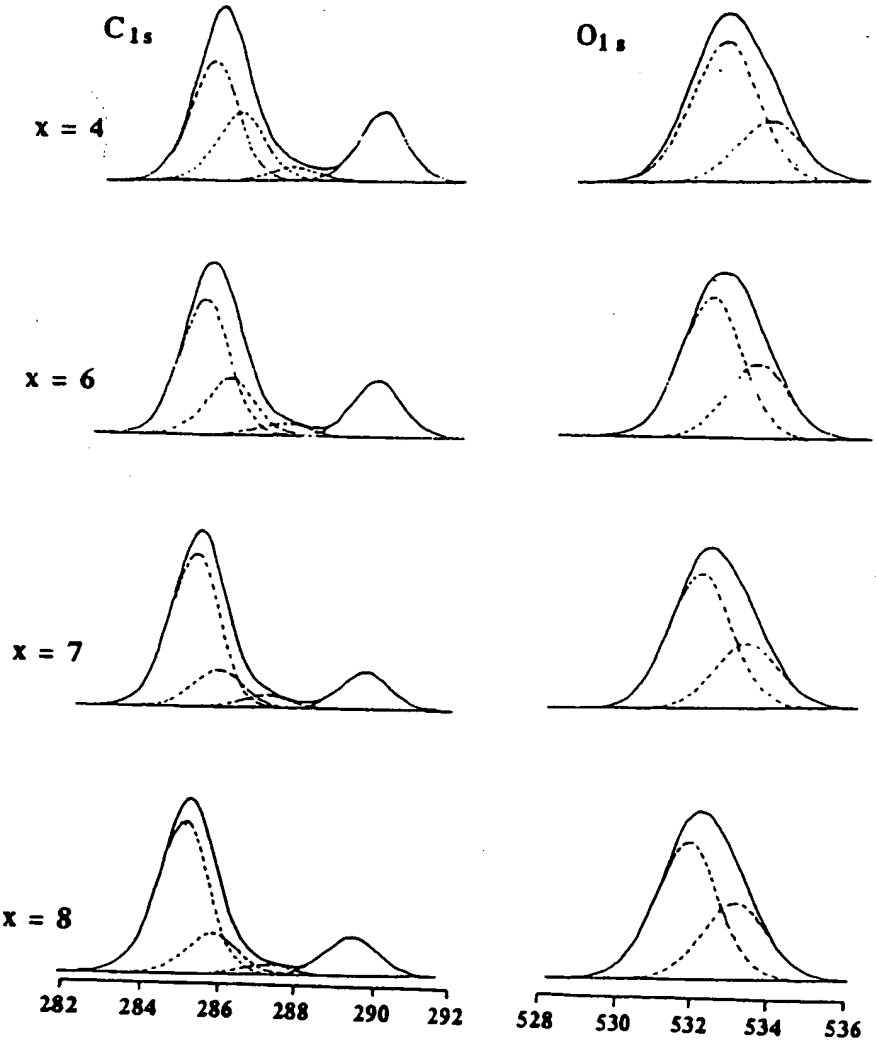


Fig. 12. The C1s, O1s core level envelopes for polyanhydrides of adipic (x = 4), suberic (x = 6), azelaic (x = 7), and sebacic acid (x = 8) (from Ref [66])

techniques, solvent removal, solvent evaporation and melt encapsulation, were analyzed by SEM. The degradation process in buffer was followed by SEM. Microspheres showed distinctive morphological characteristics induced by the fabrication method. SEM could be used in characterizing the drug release profiles and polymer degradation [67].

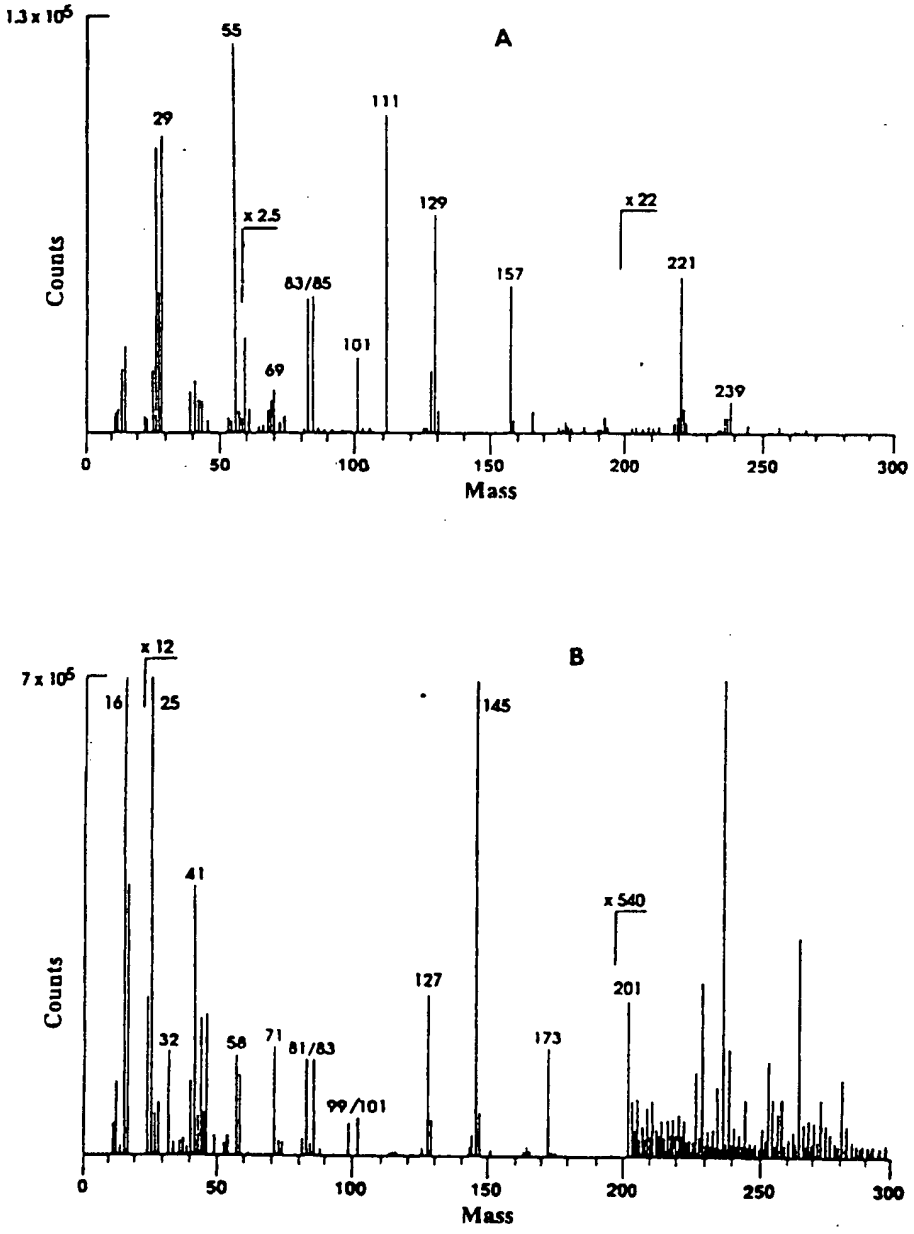


Fig. 13. Positive (A), negative (B) ion spectra of poly(adipic anhydride) (from Ref [66])

Over the last decade, SIMS and XPS have been shown to be powerful complementary techniques for determining the interfacial chemistries of polymers [68]. The surface chemical structure of aliphatic polyanhydride films has been examined using time-of-flight secondary ion mass spectroscopy (ToF-SIMS) and X-ray photoelectron spectroscopy (XPS) [65, 66]. The C1s and O1s core level spectra are displayed for the homologous series of aliphatic polyanhydrides in Fig. 12. The main peak at 285 eV corresponds to the C–H. The peak at 289.5 eV arises from O–C=O. The XPS data confirmed the purity of the surface, and the experimental surface elemental ratios were in good general agreement with the known stoichiometry of polyanhydrides.

The ToF-SIMS spectra of polyanhydrides are shown to reflect the polymer structure. The SIMS data confirms a systematic fragmentation, in both negative- and positive-ion SIMS spectra, occuring throughout the entire series of the polyanhydrides examined (Fig. 13). Radical cations were observed in the positive-ion spectra. The lower mass ranges of the negative-ion SIMS spectra contain ions at m/z 12, 13, 16, 17, 24, 25, 41, 43, and 45 that may be assigned to C–, CH–, O–, OH–, C_2–C_2H–, C_2HO–, C_2H_3O–, and CHO_2–. The ion at m/z 71 arise from the fragmentation of the anhydride unit, CH2=CHCOO– and it was seen for all polyanhydrides. At higher mass a general fragmentation pattern was observed, and the major ions are noted in Table 16.

The combined use of ToF-SIMS and XPS have shown to provide a detailed insight into the interfacial chemical structure of polyanhydrides.

Table 16. Major ions in polyanhydride SIMS spectra

Ion	PA	PSU	PAZ	PSA
positive ions				
M + H +	129	157	171	185
M +	128	156	170	184
M–OH + /MH–H_2O +	111	139	153	167
MH + CO +	157	185	199	213
M–CO_2 ±	83/85	111/113	125/127	139/141
negative ions				
M–H–	127	155	169	83
M + OH–	145	173	187	201
MH–CO_2–	173	201	215	229
M–CO_2 ± H–	83/85	–/113	–/127	–/141
M–Co ± H–	99/101	127/129	141/143	155/157
MH + CO_2 + CO–	201	–	243	–

Data taken from Ref. [66]. PA-poly(adipic acid); PSU-poly(suberic acid); PAZ-poly(azelaic acid); and PSA-poly(sebacic acid).

4 Stability

The stability of polyanhydrides in solid state and dry chloroform solution was studied [69]. Aromatic polymers such as poly(CPP) and poly(CPM) maintained their original molecular weight for at least one yeaf in solid state [69]. In contrast, aliphatic polyanhydrides such as poly(SA) and poly(phenylenedipropionic acid) (PDP) decreased in molecular weight over time (Figs. 14, 15). The decrease in molecular weight shows first-order kinetics, with activation energies of 7.5 Kcal/mole-K. The decrease in molecular weight was explained by an internal anhydride interchange mechanism, as revealed from elemental and spectral analysis (IR and ^{13}C, and ^{1}H NMR) (Fig. 16). This mechanism was supported by the fact that the decrease in molecular weight was reversible and heating of the depolymerized polymer at 180 °C for 20 min yielded the original high molecular weight polymers. Under similar conditions, an hydrolyzed polymer did not increase in molecular weight. To confirm a depolymerization process rather than hydrolysis, polymer solutions were mixed with tritiated water for 24 h, and if hydrolysis occurs, the formation of a radioactive polymer would be expected. However, no radioactive polymer was obtained although a significant decrease in molecular weight was observed [69]. The depolymerization in solution can be catalyzed by metals. Among several metals tested, copper and zinc were the most effective. It was found that the stability of polymers in the solid state or in organic solutions does not, in many cases, correlate with their hydrolytic stability. The aliphatic-aromatic homopolymers as well as the imide containing polymers also decreased in molecular weight with time which was explained by a depolymerization process [50, 52].

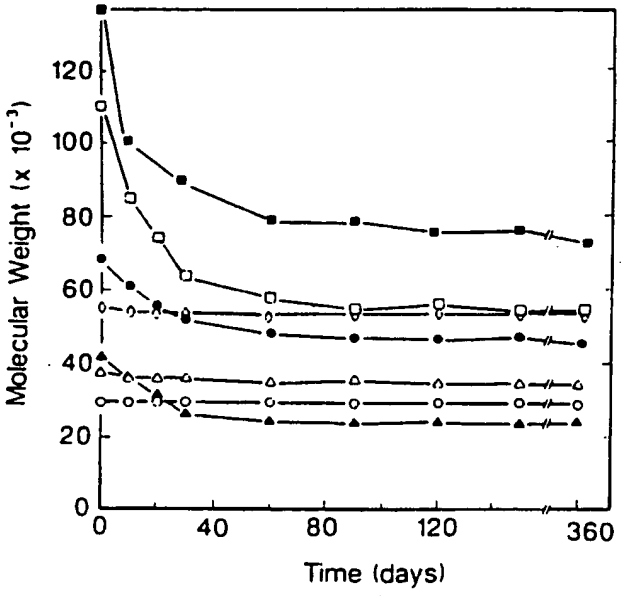


Fig. 14. Solid state depolymerization of poly(anhydrides). Weight average molecular weight of bulk poly(anhydrides) stored under vacuum at 21 °C as determined by GPC: (■) poly(SA); (□) poly(CPP-SA) 20:80; (●) poly(CPP-SA) 35:65, (◇) poly(CPP-SA) 50:50; (△) poly(CPH); (●) poly(PDP); (△) poly(CPM) (from Ref [69])

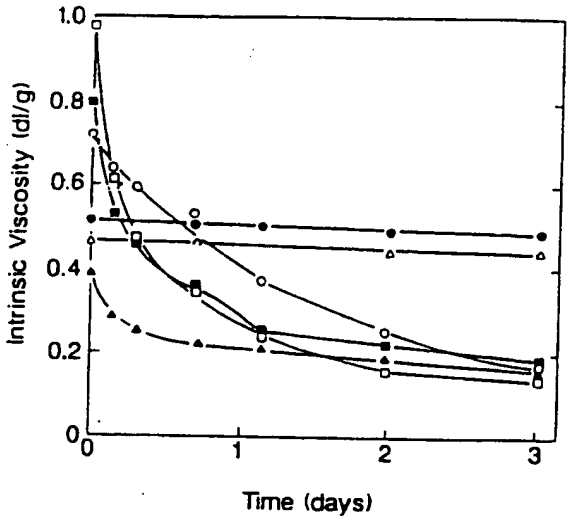


Fig. 15. Solution depolymerization of poly(anhydrides) in chloroform (10 mg/mL) stored under nitrogen at 37 °C: (□) poly(SA); (■) poly(CPP-SA) 20:80; (o) poly(CPP-SA) 50:50; (o) poly(CPH; (▲) poly(PDP); (△) poly(CPM). Viscosity was measured at 23 °C (from Ref [69] Fig. 3)

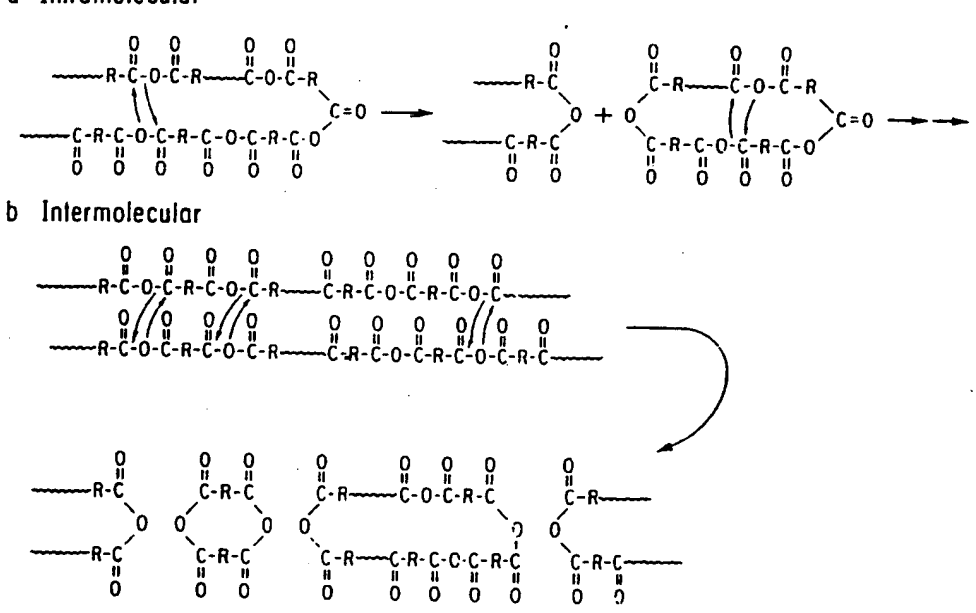


Fig. 16. Mechanism of the depolymerization of poly(anhydrides) (from Ref [69] Scheme I)

The effect of γ-irradiation on polyanhydrides for sterilization purposes has been studied. Several polymers were γ-irradiated with 2.5 Mrad dose and the properties of the polymer before and after radiation were monitored. All polymers did not change in color or pliability as well as the ^{1}H-NMR and IR spectra remain the same. The polymers did not change in molecular weight after irradiation as shown in Table 17.

Table 17. γ-Irradiation of polyanhydrides[a]

	control		γ-irradiated	
Polymer	Mw	Mn	Mw	Mn
PSA	94300	6500	78900	6000
P(FAD-SA) 1:4	40100	8700	42500	10100
P(FAD-SA) 1:1	38000	10100	40100	10000
P(FA-SA) 1:4	5100	1900	6200	2600
P(ISO-SA) 25:75	34700	6100	36100	5100

[a] Molecular weight was determined by GPC

5 In Vitro Hydrolysis and Drug Release

A drug is released from biodegradable devices by one or a combination of three processes: diffusion through the polymer matrix, dissolution of the dispersed solid drug directly into the release medium, or release of the dispersed drug by polymer surface erosion, bringing the drug along with it into solution [78, 79]. In the bioerodible systems, erosion is the release rate controlling process [79, 80]. Erosion due to polymer degradation has been classified into two types, homogeneous or bulk degradation, and heterogeneous or surface erosion [79, 80].

In homogeneous or bulk erosion, the release medium penetrates the entire matrix and degradation occurs at the same rate on the surface and in the bulk. In this scenario, drug release is initially delayed and quite slow; however, as the bulk matrix starts eroding, the release rate increases significantly. Therefore, in bulk erosion, the release is not zero order, and it is essentially independent of the device geometry. The poly(lactic acid) and poly(lactic-glycolic acid) polymers belong to the class of bulk eroding polymers, and the release from these devices exhibits the profile expected for bulk erosion [79].

In contrast, the surface eroding polymers are hydrophobic, resist penetration of water into the bulk matrix, and hence the release medium degrades and erodes only the surface of the matrix [79]. Therefore, the release rate is affected by the surface-to-volume ratio, the geometry of the device, and drug loading. If the surface area of the eroding surface remains constant, drug release would be zero order. In addition, release rate is directly proportional to drug loading, and the lifetime of the device is directly proportional to device thickness [79].

Poly(ortho ester)s were the first polymers used to prepare surface eroding devices, but additional excipients such as acid anhydrides or basic excipients in the interior of the matrix, had to be used to prevent bulk erosion [79, 81].

The degradation of polyanhydrides, in general, varies with a number of factors, such as:

1. The chemical nature of the monomer used to produce the polymer
2. In a series of copolymers, the relative amounts of the two monomers used to produce the polymer

3. The hydrophobicity and loading of the drug in the polymeric matrix
4. The pH of the surrounding medium (the higher the pH, the more rapidly the materials degrade)
5. The shape and geometry of the implant (the degradation is dependent on the surface area)
6. The accessibility of the implant to water (porous materials will degrade more rapidly than non-porous)
7. The method of manufacture for the material (e.g. compression-molded materials will degrade more rapidly than injection-molded)

The degradation rates for a number of polyanhydrides are available in the literature [1, 82, 83]. However, recently, a new class of polyanhydrides poly(FAD-SA) have been synthesized from non-linear hydrophobic dimer of oleic acid or erucic acid and relatively hydrophilic sebacic acid. This copolymer can be prepared in various ratios of the monomers to achieve the desired degree of hydrophobicity; increasing the percentage of FAD, a more hydrophobic copolymer, is obtained. Another advantage of this copolymer is its ability to be formulated as films, microspheres, and beads [84].

To study the release characteristics and the mechanism of drug release from P(FAD-SA) devices, a study was conducted employing bupivacaine as a model drug. Bupivacaine, a hydrophobic weak base (pKa = 8.2) is used for local anesthesia [85]. In several clinical situations, a prolonged local anesthetic effect is desired. Hence, a controlled release formulation of bupivacaine would be useful. Five copolymers, P(FAD-SA) 10:90, 20:80, 30:70, 50:50 and 80:20, with varying degree of hydrophobicity and erosion rates, (10:90 being more hydrophilic than 30:70) were used to fabricate the devices. Bupivacaine hydrochloride was dispersed in the melted copolymers at 10% W/W load. The devices, 200 mg in weight, in the shape of rectangular blocks, with dimensions of $1.3 \times 0.7 \times 0.5$ cm were prepared by the melt casting technique. The drug loading per unit volume was therefore, 0.044 gm/cm^3 of the device. The drug release profiles were determined at pH 7.4, and analyzed by the surface erosion based model [78, 80] as described below.

Various mathematical models have been developed to predict drug release behavior from degradation controlled monolithic systems [78–80]. A model for predicting drug release from erodible devices of various geometries developed by Hopfenberg was used for data analysis of this study [78]. This model assumes an agent uniformly dispersed in the matrix, with the drug release primarily occurring due to degradation/erosion of the matrix [78, 80].

The equation for cumulative drug release from an erodible cylinder shaped device with radius r and length h is given by Eq. (1):

$$M_t = 2\pi C_o hBt[r - (Bt/2)] \quad (1)$$

where,

Co = Drug load in gm/cm^3
B = Erosion rate of the polymer device in cm/day
t = Time in days

The equation for the fractional agent release versus time is given by the following expression:

$$M_t/M_\infty = 2(t/t_\infty) - (t/t_\infty)^2 \qquad (2)$$

The devices prepared in our study were almost cylindrical in shape because the two smaller dimensions were very similar (0.5 and 0.7 cm). The devices were equivalent to a cylinder both in terms of surface area and volume, with a radius of 0.33 cm and a length of 1.3 cm, and they could thus be classified as erodible cylindrical devices with dispersed drug. Therefore, Eqs. (1) and (2) are applicable and should describe the release profile. To determine if drug release from the devices was controlled by surface erosion, the release profiles were fitted to Eq. (1). Since all the parameters in Eq. (1) except B (the erosion rate) are known, nonlinear regression was used on the release profiles to obtain the optimized values of B.

The release profiles were also independently evaluated for the type of release kinetics observed; i.e. zero order, SQRT of time and first order release. It appeared that for all the copolymers studied, the release was best described by first order release kinetics. The release profiles were thus fitted to the following equation to obtain the first order release rate constant, Kr:

$$\%\text{Cum. Drug Rel.} = M_t = 100[1 - \exp(-k_r t)] \qquad (3)$$

The Kr observed was then correlated with the erosion rate constant (B) to determine if drug release is controlled by polymer erosion.

The cumulative release profile of bupivacaine from the various copolymer devices are shown in Figs. 17a and 17b. The drug release occurred very slowly over a period of 15–25 days depending on the polymer used. The fractional agent release (M_t/M_∞) was very well described by Eq. (2) and the coefficients of the various terms in Eq. (2) were determined by polynomial regression for all the copolymers studied. The equation best describing the release profiles is as shown below:

$$M_t/M_\infty = (1.99 \pm 0.11)t/t_\infty - (1.19 \pm 0.53)(t/t_\infty)^2 \qquad (4)$$

$n = 8$ and $R^2 > 0.998$ for all copolymers.

Equation (4) is very similar to the theoretically derived Eq. (2) in the form and the coefficients, suggesting that the release is surface erosion controlled.

The release profiles were also fitted to Eq. (1) using a nonlinear regression program to obtain estimates of B, the erosion rate. R^2 in all cases was greater than 0.99 and hence the good fit of the release profile to Eq. (1). The optimized values of B obtained by nonlinear regression are listed in Table 18. The erosion rate ranged from 0.0037 cm/day for the most hydrophobic copolymer. P(FAD-SA) 80:20 to 0.028 cm/day for the most hydrophilic copolymer, P(FAD-SA) 10:90. However, the erosion rate was not linearly dependent on the hydrophilicity of the polymer, expressed as % of sebacic acid in the copolymer (Fig. 18).

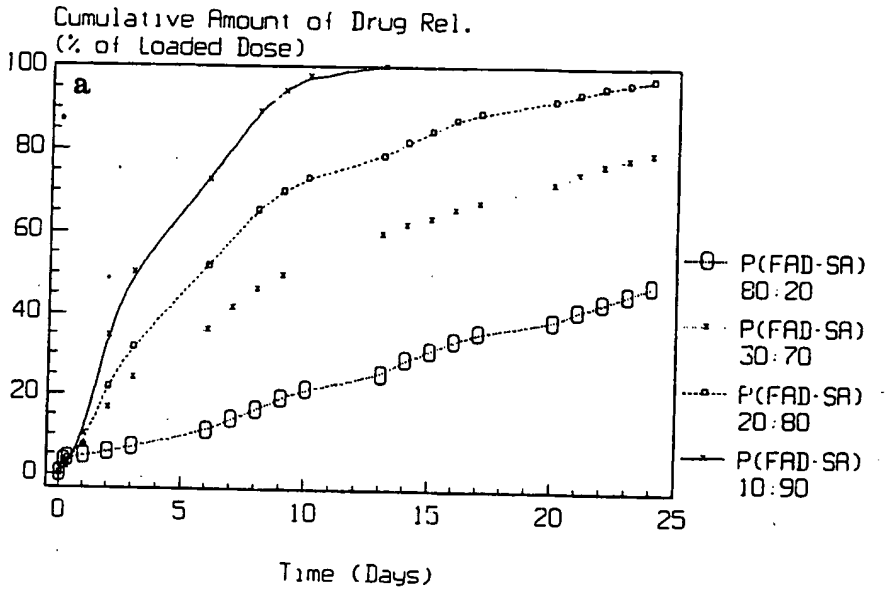


Fig. 17a. Release profiles of bupivacaine hydrochloride from polyanhydride copolymer devices at pH 7.4

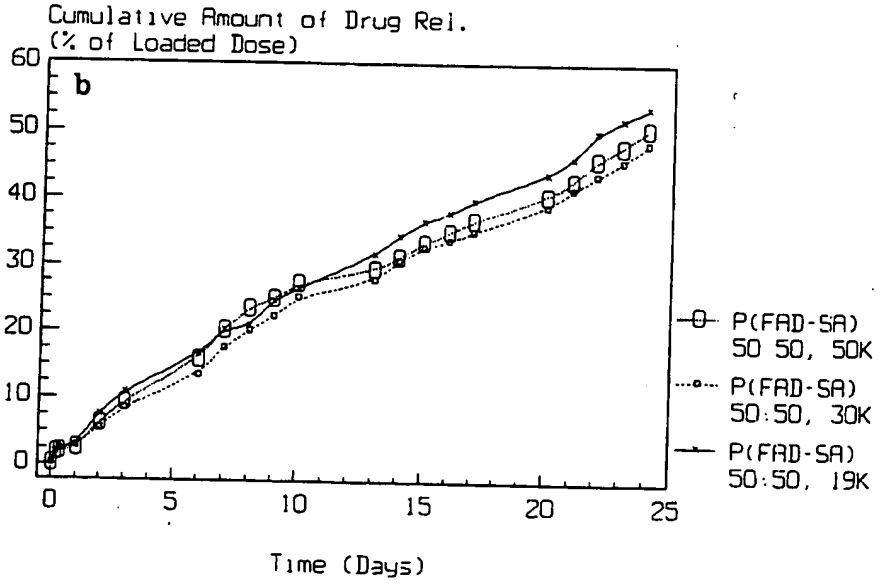


Fig. 17b. Release profiles of bupivacaine hydrochloride from P(FAD-SA) 50:50 devices with different initial molecular weights of the copolymer, at pH 7.4

The dependence was hyperbolic with very little effect of the sebacic acid content on erosion rate between 20–50% sebacic acid. However above 50% sebacic acid, the erosion rate increased very rapidly with a small increase in the hydrophilicity of the copolymer. This results also demonstrate that by varying the ratio of

Table 18. Parameters for release of bupivacaine hydrochloride from polyanhydride devices at pH 7.4

Copolymer used to prepare the device	Erosion rate cm/day	Drug release rate due to erosion, $B^{*}Co$ gm/cm^2/day	First order release rate constant, Kr, Day^{-1}
P(FAD-SA) 80:20 MW 72000	0.0037	0.00016	0.025
P(FAD-SA) 50:50 MW 19000	0.0044	0.00019	0.031
P(FAD-SA) 50:50 MW 30000	0.0039	0.00017	0.0027
P(FAD-SA) 50:50 MW 50000	0.0041	0.00018	0.029
P(FAD-SA) 30:70 MW 55000	0.009	0.00037	0.07
P(FAD-SA) 20:80 MW 107600	0.015	0.00068	0.13
P(FAD-SA) 10:90 MW 225000	0.028	0.0012	0.24

monomers in the copolymer, a wide range of erosion rates can be produced to get the desired drug release rates [87].

The release profiles could not be adequately described by either zero or SQRT of time order kinetics, but the release profiles were well described by first

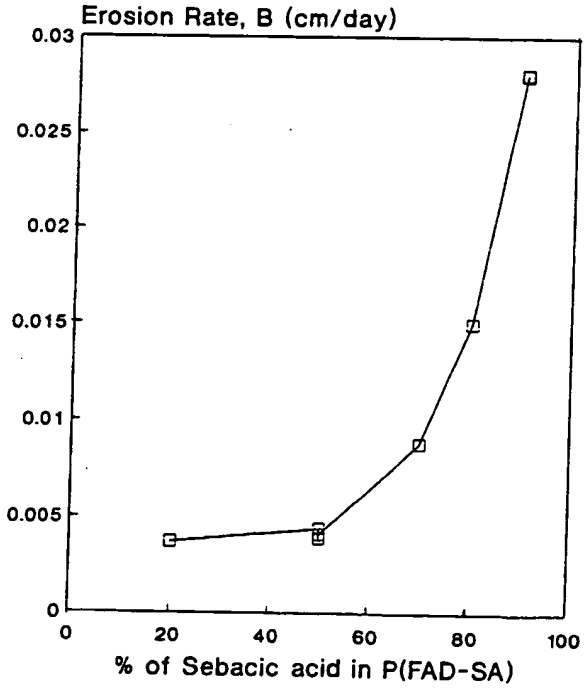


Fig. 18. Dependence of erosion rate estimated from Eq. (1) on the hydrophilicity of the P(FAD-SA) copolymer expressed as % of the sebacic acid content

order kinetics as seen from Fig. 19. The R^2 values for all the release profiles were greater than 0.99, and the optimized values of K_r, the first order release rate constant obtained are also listed in Table 18. K_r appeared to depend on the hydrophilicity of the copolymer in the same fashion as erosion rate. There was excellent linear correlation between Kr and the erosion rate as shown in Fig. 19. The linear relationship between erosion rate and Kr could be described by the following equation:

$$K_r = 8.73B - 0.007, \quad R^2 = 0.9996 \tag{5}$$

This indicates that Kr is linearly dependent on erosion rate of the polymer suggesting that erosion rate solely controls and determines the rate of drug release from the device.

The polymer degradation data expressed as a decrease in the molecular weight and weight loss of the device was available for only one of the copolymers studied, P(FAD-SA) 10:90. The release of drug was correlated with polymer degradation by plotting the % cumulative drug released and the % decrease in molecular weight as shown in Fig. 20. As can be observed from this figure, while the molecular weight of the copolymer decreases by 80% in the first two days, only 20% drug is released. Subsequently, the copolymer degradation slows down, yet drug release continues at a fairly slow first order rate for 24 days. This

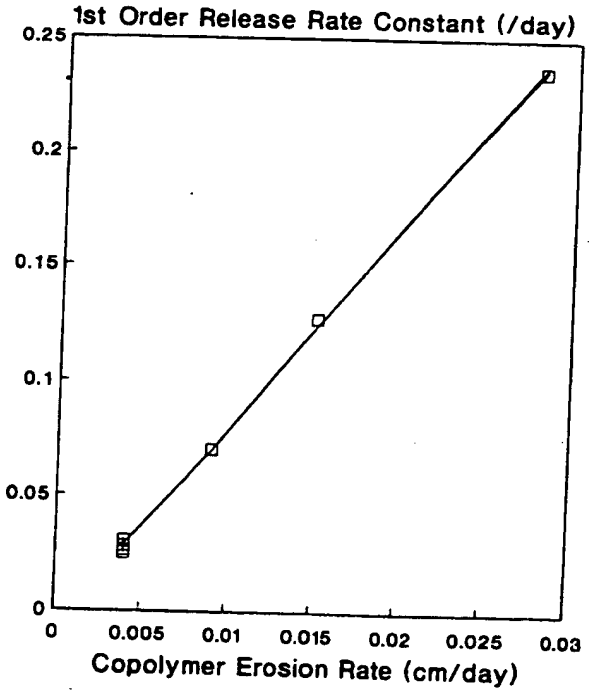


Fig. 19. Correlation of first order release rate constant with erosion rate of the P(FAD-SA) device

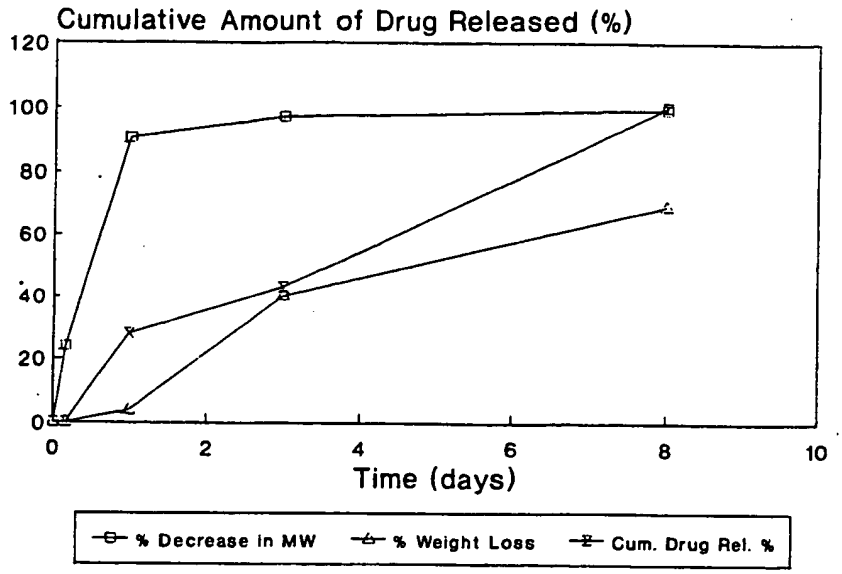


Fig. 20. Correlation of drug release with copolymer degradation expressed as % decrease in molecular weight of the copolymer P(FAD-SA) 10:90 and the weight loss of device

was not a direct correlation between the % decrease in molecular weight and % drug released. However, much better correlation between drug release and polymer degradation (expressed as % decrease in the weight of the device) was observed (Fig. 20). The P(FAD-SA) 50:50 devices were prepared with different initial molecular weights of the copolymer (Table 18). The initial molecular weight of the copolymer appeared to have no effect on drug release (Fig. 17b), and also on erosion rate (Fig. 18, Table 18).

The erosion in polyanhydride matrices has been reported to be purely surface of the heterogeneous type, and the results of this study support the past observation [82]. No lag time for drug release was found, as observed also for poly-lactic acid and poly-lactic acid-glycolic acid, which have been known to undergo bulk erosion [79]. In addition, fit of the data to Eqs. (1) and (2) (which have been derived for a surface eroding polymer), confirm the surface eroding nature of the polyanhydrides.

The erosion rates estimated are as expected and drug release rates calculated from the erosion rates are in the same order of magnitude as those reported by Leong et al. [83]. The expected drug release rates based on erosion are in units of $gm/cm^2/day$, and thus one would expect zero order release rates for any incorporated drug from a unit surface area of the device. This would be the case, if the surface area of the device remained constant throughout the release period. In the case of the cylinder, the surface area is constantly reducing as the device is eroding at a constant rate. Therefore, despite the constant erosion rate of the polymer, release rate of drug decreases steadily. This results in a first order rate

of drug release. If the devices were designed in the shape of a slab or a disk, the surface area exposed to the release medium would be constant, as well as the release rate, i.e. zero order release.

The strong correlation observed between K_r and erosion rate indicates that erosion is the major mechanism for drug release. In fact, a priori knowledge of the erosion rate of a polymer could be used to predict the release profile of the drug from a similar device or from a device of a known geometry. The erosion rate appears to be dependent on the hydrophilicity of the copolymer but not linearly. Increasing content of sebacic acid increases the hydrophilicity of the polymer [82], which results in a higher erosion rate and hence higher release rate. This could be explained by the fact that the anhydride linkages in the polymer are hydrolyzed subsequent to penetration of water into the polymer. The penetration of water or water uptake depends on the hydrophobicity of the polymer and therefore, the hydrophobic polymers which prevent water uptake, have slower erosion rates and lower drug release rates [88, 89]. This is valuable information since one can alter the hydrophobicity of the polymer by altering the structure and/or the content of the copolymer, thereby being able to alter the erosion rate. Since in the P(FAD-SA) series of copolymers, a 10 fold increase in erosion rate was achieved by alteration of the ratio of the monomers, P(FAD-SA) can be used to deliver drugs over a wide range of release rate.

There was no correlation between drug release and polymer degradation expressed as % decrease in the molecular weight, which may appear to be self-contradictory. However, on closer examination, it appears that drug dispersed in the polymer matrix is released when the polymer matrix erodes bringing the drug with it into solution. Thus the release rate would depend on the rate of erosion expressed as volume of the matrix dissolved per unit time, times the drug load. The implication being that weight loss should correlate with drug release and it is a more appropriate indicator of erosion rate than the % decrease in molecular weight. Another fact is that in surface erosion, the molecular weight of the polymer at the surface may decrease but the interior of the device may still have the same molecular weight. Secondly, the lower molecular weight fragments may not diffuse out or dissolve into the release medium. Therefore, it is not the decrease in molecular weight but the weight loss subsequent to the decrease in molecular weight, and the diffusing out of the low molecular weight fragments, which correlates with drug release. This also explains why drug release from P(FAD-SA) 50:50 devices, was independent of the initial molecular weight of the copolymer (Fig. 17b and Table 18).

6 Biocompatibility and Toxicology

The eventual clinical use of any synthetic polymeric material requires adequate testing for safety, toxicity, and biocompatibility of the specific polymer matrix, as a direct contact between the polymer and biological tissues is evident, and

potential undesired tissue-implant interactions might occur. In the case of biodegradable matrices, not only the possible toxicity of the polymer has to be evaluated, but also the potential toxicity of breakdown products. The last section of this chapter reviews existing data about the biocompatibility, safety, and toxicity of polyanhydride polymers actually available for biomedical applications.

The polyanhydrides constitute so far the only class of surface-eroding polymers approved for clinical trials by the Food and Drug Administration. In one of the first detailed reports on biocompatibility and toxicology of polyanhydrides published in 1986, several accepted criteria and tests to evaluate new biomedical materials were used to assess the safety of polyanhydrides [90]. In this study, poly [bis(*p*-carboxy-phenoxy) propane anhydride [P(CPP)], poly (terephtalic acid anhydride) (PTA), and their copolymers were tested. Neither mutagenicity nor cytotoxicity was associated with the polymers or their degradation products, as evaluated by mutation assays [90]. The products also gave a negative response in an in vitro teratogenicity test [91]. The tissue response of these polyanhydrides was studied by subcutaneous implantation in rats and in the cornea of rabbits. The polymers did not provoke inflammatory responses in the corneas over a six week implantation period [90]. The authors also reported no evidence of inflammatory cells after the subcutaneous implantation in rats over a six month period, and only slight tissue encapsulation by layers of fibroblastic cells was observed [90]. Growth of two types of mammalian cells in tissue culture was also not affected by the polyanhydride polymers; both the cellular doubling time and cellular morphology were unchanged when either bovine aorta endothelial cells or smooth muscle cells were grown directly on the polymeric substrate.

Additional evidence of polyanhydride biocompatibility was provided from 8 weeks subcutaneous implantation in rats of high doses of the 20 : 80 copolymer of CPP and SA. Prenecropsy examination of all rats revealed no clinical evidence of induced changes in physical appearance or activity due to implantation of the polymer [92]. Histological evaluation indicated relatively minimal tissue irritation with no evidence of local or systemic toxicity [92]. Systemic response to the polymer was evaluated by monitoring of blood chemistry and hematologic values, and by comprehensive examination of organ tissues. Both methods revealed no significant response to the polymer [92].

Since the PCPP-SA polyanhydride copolymer was designed to be used clinically to deliver an anticancer agent directly into the brain for the treatment of brain neoplasms, in vivo safety evaluations and brain biocompatibility were assessed with rats [93], rabbits [94], and monkeys [95]. In the rat brain study, the tissue reaction of the polymer (PCPP-SA 20:80) was compared to the reaction observed with two standard materials used in surgery, which have been extensively studied. These materials are Gelfoam (absorbable gelatin sponge), and Surgicel (oxidized cellulose absorbable hemostat commonly used in brain surgery). Histological evaluation of the tissue demonstrated a small rim of necrosis around the implant, and a mild to marked cellular inflammatory

reaction limited to the area immediately adjacent to the implantation site, slightly more pronounced than Surgicel at the earlier time points, but noticeably less marked than Surgicel at the later times [93]. The reaction to Gelfoam was essentially equivalent to that observed in control rats.

In the rabbit brain safety study using P(CPP-SA) 50:50 copolymer, even less of an inflammatory reaction was observed, and the polymer was essentially equivalent to Gelfoam [94]. In a similar brain biocompatibility study conducted in monkeys, no abnormalities were noted in the computer tomography scans and magnetic resonance images, nor in the blood chemistry or hematology evaluations [95]. No systemic effects of the implants were observed on histological examinations of any of the tissues tested [96]. No unexpected or untoward reactions to the treatments were observed.

Recently, new classes of polyanhydrides have been synthesized and are undergoing extensive preclinical testing, including a wide range of toxicity and biocompatibility studies. Examples of these new polyanhydrides materials are polymers of sebacic acid (SA), and 1:1 copolymers of SA with fatty acid dimer [P(FAD:SA)], fumaric acid [P(FA:SA)], and 20:80 copolymer of SA with isophthalic acid [P(IPA:SA)] [97]. These new polyanhydrides were implanted intramuscularly, subcutaneously and in the cornea of rabbits, and ocular and muscle irritation studies were performed. The results were compared to those obtained with the previously mentioned standard materials Gelfoam and Surgicel, and with Vicryl, a synthetic absorbable suture [97]. No significant clinical signs or abnormalities of the incision sites were observed during the study period (4 weeks). No meaningful differences could be seen in reaction between the various polymer implants tested and the control materials [97]. In the cornea study, no evidence of inflammatory response was observed with any of the implants at any time. On an average, the bulk of the polymers disappeared completely between 7 and 14 days after implantation [97].

The new FAD-SA anhydride copolymers were used to deliver water soluble anticancer agents such as, carboplatin, 4-hydroperoxycyclophosphamide (4HC), and methotrexate to the rat brain [98]. In vitro release kinetics studies conducted on polymer matrices containing these drugs have shown sustained release of the drugs over a period of 3 to 5 weeks. This is particularly important for the delivery to the brain in that the blood-brain barrier effectively blocks most water soluble drugs from entering the brain. The safety and biocompatibility of these polymers in the rat brain were compared with that of Surgicel and Gelfoam. The localized inflammatory response generated by the p(FAD-SA) polymer was comparable to that of Surgicel, but more pronounced than the reaction evoked by Gelfoam [99].

With these preclinical toxicology and biocompatibility studies carried out in animals having demonstrated both the efficacy and safety of the polyanhydrides, studies involving these materials moved toward human clinical use. In 1987, the Food and Drug Administration approved experimental use of these polyanhydrides in humans, under an Investigational New Drug clinical trial application. A Phase I/II clinical trial of 21 patients in five U.S. hospitals was carried out

showing the safety and no toxicity of these polymers either clinically or pathologically, and extending patient life time beyond conventional drug treatment [23]. In these clinical studies, a polyanhydride dosage form (Gliadel) consisting of wafer polymer implants of 20:80 poly(CPP-SA) and containing the chemoherapeutic agent Carmustine (BCNU) were used for the treatment of glioblastoma multiforme, a universally fatal form of brain cancer. In these studies, up to eight of these wafer implants were placed to line the surgical cavity created during the surgical removal of the bulk of the brain tumor in patients undergoing a second operation for surgical debulking of either a Gradè III or IV anaplastic astrocytoma. Following surgery the BCNU is then released directly into adjoining tissues that may contain cancer cells not removed during surgery. The safety of this polyanhydride copolymer implanted into these patients has been demonstrated. No central or systemic side effects of doses of BCNU which would produce marked effects on the hemopoietic system when injected intravenously were observed. No adverse reactions to the BCNU wafer treatment itself were found. Based on these results, further studies designed to measure the efficacy of this approach to the treatment of brain cancer is currently underway in a Phase III study in 32 U.S. and Canadian hospitals [95, 96].

7 Applications

Applications of Polyanhydrides have been reviewed [1, 22]. A comprehensive review on polyanhydride applications is in preparation [6].

Anticancer agents were incorporated in polyanhydride wafers and used for site-specific chemotherapy for the treatment of brain tumors [22, 91–102]. BCNU has been the primary drug in this application. In the past 3 years investigations have expanded to new polymers and other drugs such as 4HC, cisplatin, carboplatin, and several alkaloid based drugs to develop a better system for the treatment of brain tumors [100]. Carboplatin incorporated in poly(FAD-SA), prepared by mixing the drug in the melted polymer, showed promising result in treating brain tumors in laboratory animals [102]. The same polymer has been used for the delivery of gentamicin sulfate for the treatment of osteomyelitis [21]. Gentamicin was released for more than two weeks both in vivo and in vitro. This device in a form of linked beads is now considered for human clinical trials. The effect of long term glutamic acid stimulation of trigeminals motoneurons, using poly(FAD-SA) microspheres was studied. The study was undertaken to determine the role of glutamate in possible growth disorders of the craniofacial skeleton. Rats receiving glutamate showed pronounced skeletal changes in the snout region, showing that sustained release of glutamic acid in vivo can effect the developing skeleton in growing rats [103]. Poly(FA-SA) microspheres containing an antiinflammatory drug dispersed in a biocompatible organic vehicle have been used as eye drops for extended drug

action. The microspheres were not irritating to the rabbit eye and lasted in the eye for 6 to 10 hours. The polymer was completely degraded and dissolved within 24 hours both in vitro and in vivo.

8 Conclusion and Future Directions

The chemistry of polyanhydrides has been considerably developed and a large selection of polymers are available for the applications at hand. We now have a better understanding on how these polymers degrade and release the drug under physiological conditions. The drug release from these polymers is controlled by polymer hydrolysis and by diffusion, where the ratio between the two processes depends largely on the chemistry of the polymer, the fabrication method, the geometry of the device and the drug properties. Extensive toxicology information on a range of polyanhydrides is available, which indicate that most polyanhydrides prepared from pure common diacids are biocompatible. Various fabrication and preparation methods are available, and some polymers and devices have been produced in large quantities in a cost effective process. Future studies should concentrate on finding new medical applications using polyanhydrides. These polymers are particularly useful in local delivery of drugs for periods of several weeks in a form of an implant or film.

Acknowledgments. This work was supported in part by The Eliahu and Tatiana Leszczynski Research Foundation and The Robert szold institute for Applied Science of the P.E.F Israel Endowment Funds Inc. Dr. Domb is affiliated with the Blum Center for Pharmacy, The Hebrew University of Jerusalem.

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Received 12 August 1992